PROSPECTIVE STUDY OF NATURAL HISTORY, FOLLOW- UP, TREATMENT AND OUTCOME OF PATIENTS WITH GESTATIONAL TROPHOBLASTIC DISEASE AT IOG

Dissertation submitted to

THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY

In partial fulfillment of the regulations
for the award of degree of

M.D. DEGREE EXAMINATION

OBSTETRICS AND GYNECOLOGY

BRANCH – II

INSTITUTE OF OBSTETRICS AND GYNECOLOGY,
HOSPITAL FOR WOMEN AND CHILDREN, EGMORE
CHENNAI-8

APRIL 2012

CERTIFICATE

This is to certify that the dissertation entitled **"PROSPECTIVE STUDY OF NATURAL HISTORY, FOLLOW- UP, TREATMENT AND OUTCOME OF PATIENTS WITH GESTATIONAL TROPHOBLASTIC DISEASE AT IOG"** presented here is the bonafide original work done by **Dr.Raajem.S.R.** at the Institute of Obstetrics and Gynecology, Egmore, Chennai 600008 , in partial fulfillment of the regulation for the award of degree of **M.D, Obstetrics and Gynecology,** Branch-II submitted to The Tamil Nadu Dr.MGR Medical University for examinations to be held in April 2012.

Prof.M.Mohanambal,
M.D., D.G.O.,
Director & Head Of the Department
Institute of Obstetrics & Gynecology
Hospital for Women and Children,
Egmore, Chennai-8

Dr.V.Kanagasabai,
M.D.,
Dean,
Madras Medical College
and Research Institute
Rajiv Gandhi Govt. General Hospital,
Chennai-3

Prof.K.Kalaichelvi,
M.D., D.M.,
Department of Medical Oncology,
Institute of Obstetrics & Gynecology
Hospital for Women and Children,
Egmore, Chennai-8.

Prof. Jayashree Srinivasan
M.D., D.G.O., D.N.B.,
Institute of Obstetrics &
Gynecology, Hospital for Women and
Children, Egmore, Chennai-8.

,

DECLARATION

I **Dr.Raajem.S.R,** solemnly declare that this dissertation entitled, **"PROSPECTIVE STUDY OF NATURAL HISTORY, FOLLOW- UP, TREATMENT AND OUTCOME OF PATIENTS WITH GESTATIONAL TROPHOBLASTIC DISEASE AT IOG"** is a bonafide work done by me in The Institute of Obstetrics and Gynecology and Hospital for Women and Children, Egmore , Chennai -8, for the degree of M.D. Obstetrics and Gynecology.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, towards partial fulfillment of the regulations for the award of M.D. Degree in Obstetrics and Gynecology.

Place: Chennai Signature of the Candidate

Date: (**Dr.Raajem.S.R)**.

Prof.M.Mohanambal,M.D.,D.G.O.,
Director & Head of the Department,
Institute of Obstetrics &Gynecology
Hospital for Women and Children,
Egmore, Chennai-8

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3
Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Raajem .S.R
PG in MD OG
Institute of Obstetric & Gynaecology, Egmore, Chennai -3.

Dear Dr. Raajem S.R

The Institutional Ethical Committee of Madras Medical College reviewed and discussed your application for approval of the project / proposal / clinical trail entitled "Prospective analysis of natural history, follow-up , treatment and outcome of patients with gestational trophoblastic diseases at I.O.G" No 25082010.

The following members of Ethical committee were present in the meeting held on 17.08.2010 conducted at Madras Medical College, Chennai -3

1. Prof. S.K. Rajan, MD -- Chairperson
2. Prof. J. Mohanasundaram, MD,Ph.D,DNB -- Deputy Chairman
   Dean, Madras Medical College, Chennai -3
3. Prof. A. Sundaram, MD -- Member Secretary
   Vice Principal , MMC, Chennai -3
4. Prof R. Nandhini, MD -- Member
   Director, Institute of Pharmacology, MMC, Ch-3
5. Prof. Pregna B. Dolia , MD -- Member
   Director, Institute of Biochemistry, MMC, Ch-3
6. Prof. C. Rajendran , MD -- Member
   Director, Institute of Internal Medicine, MMC, Ch-3 -- Member
7. Prof. V. Shruti Kamal, MS -- Member
   Professor of Surgery, MMC, Ch-3
8. Mrs. Arnold Saulilna, Social Scientist -- Member

We approve the trail to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank **Dr.V.Kanagasabai,M.D.,** Dean, Madras Medical College and Research Institute, Chennai – 600 003 and **Dr.M.Mohanambal,M.D.,D.G.O.**, Director and Superintendent, Institute of Obstetrics and Gynecology, Egmore, Chennai for granting me permission to utilize the facilities of the Institute for my study.

I am extremely grateful to our Director and Superintendent, Professor and Head of the Department of the Institute of Obstetrics and Gynecology , **Dr. M. Mohanambal,M.D.,D.G.O.**, for her professional support and encouragement to do my thesis.

I thank my former Directors **Dr.Revathy Janakiraman,M.D.,D.G.O.,** and **Dr.Radha Bai Prabhu,M.D.,D.G.O.**, for leading me to work on this dissertation and for their constant motivation.

I owe my deepest gratitude **to Dr.K.Kalaichelvi,M.D.,D.M.**, Professor of Oncology, for her supervision, advice, and guidance from the very early stage of this thesis. I appreciate all her contributions of time and ideas to make my thesis experience productive and stimulating. I am also thankful for the excellent example and inspiration she has provided as a successful oncologist and professor. Her immense knowledge, insightful comments and enlightening questions has guided me at all times.

I would like to express my sincere thanks to **Dr. Jayashree Srinivasan M.D.,D.G.O.,D.N.B.**, for her consistent encouragement and guidance .Her wisdom, valuable criticisms and stimulating suggestions has helped me to write this thesis.

I owe my thanks to all unit chiefs, and civil assistant surgeons for their constant support, valuable help and guiding assistance.

I am indebted to all my patients for their co-operation, without whom it would have been impossible for me to do this thesis.

CONTENTS

INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a spectrum of disorders characterized by an abnormal proliferation of trophoblastic tissue after a normal or abnormal fertilization with varying propensity to spontaneously regress, locally invade and metastasize.

Hydatidiform mole is the most common form of GTD, and can be subdivided into

- Complete mole (CM)
- Partial mole (PM)

The malignant forms are

- Invasive mole
- Choriocarcinoma(CC)
- Placental site trophoblastic tumor(PSTT)
- Epithelioid trophoblastic tumor (ETT)

Hydatidiform mole and invasive mole are villous forms of GTD and choriocarcinoma and PSTT are non villous forms of GTD.

There are wide variations in the incidence and epidemiological factors worldwide and there are changing trends in clinical presentation and management. This implicates the need for region specific studies of GTD.

Gestational trophoblastic neoplasms are one of the most curable of all solid tumors with cure rates more than 90% with fertility retention even in the presence of widespread metastasis.

This success can be explained by the use of serum β hCG as a biomarker for follow up and development of effective chemotherapy regimens.

In UK all patients are included in a national register with a central pathologic review. As there are no registries for trophoblastic disease available in India, the actual incidence of GTD is not known.

It is important to analyze the natural history, follow up, treatment and outcome of this unique condition. This will help making decisions and optimizing management and preventing treatment failure.

OVERVIEW OF GESTATIONAL TROPHOBLASTIC DISEASE

Hippocrates was probably the first to describe gestational trophoblastic disease around 400 BC in his description of dropsy of the uterus.

In 1276, Margret, Countess of Henneberg delivered some 365 children, baptized in two basins, boys being christened John and girls Elizabeth.

Marchand first associated hydatidiform mole with pregnancy in 1895. The etymology is derived from *hydatisia* ("a drop of water"), referring to the watery contents of the cysts, and *mole (*“millstone”), meaning false conception.

Healthy trophoblastic tissue aggressively invades the endometrium and develops a rich uterine vasculature, generating an intimate connection between the fetus and the mother known as the placenta.

Trophoblasts (from Greek *trephein*: to feed, and *blastos*: germinator) are cells forming the outer layer of a blastocyst, which provide nutrients to the embryo and develop into a large part of the placenta. Trophoblasts are specialised cells of the placenta that play an important role in embryo implantation and interaction with the decidualised maternal uterus. The trophoblast proliferates and differentiates into 2 cell layers at approximately 6 days after fertilization.

Layer	Location	Description
cytotrophoblast	inner layer	Single celled, inner layer of the trophoblast.
syncytiotrophoblast	outer layer	Thick layer that lacks cell boundaries and grows into the endometrial stroma. It secretes β hCG in order to maintain progesterone secretion and sustain a pregnancy.
intermediate trophoblast (IT)	implantation site, chorion & villi (dependent on subtype)	anchor placenta (implantation site IT), unknown (chorionic & villus IT)

Cytotrophoblast is considered to be the trophoblastic stem cell; it differentiates into the other forms of trophoblastic tissue (intermediate trophoblast and syncytiotrophoblast).

Syncytiotrophoblast is a unique multi nucleated layer, lacks proliferative capacity and is maintained by fusion of underlying cytotrophoblast cells. They massively increase the surface area available for nutrient exchange between the mother and the fetus.

Intermediate trophoblasts are thought to be the cell of origin for Exaggerated placental site (EPS),Placental site nodule (PSN),Placental site trophoblastic tumour (PSTT) and Epithelioid trophoblastic tumour (ETT).

Gestational trophoblastic disease represents a form of proliferation of trophoblasts.

Malignant-like behaviour is tightly controlled in healthy trophoblast. However, in gestational trophoblastic disease the regulatory mechanisms fail, resulting in tumors that are highly invasive, metastatic and very vascular.

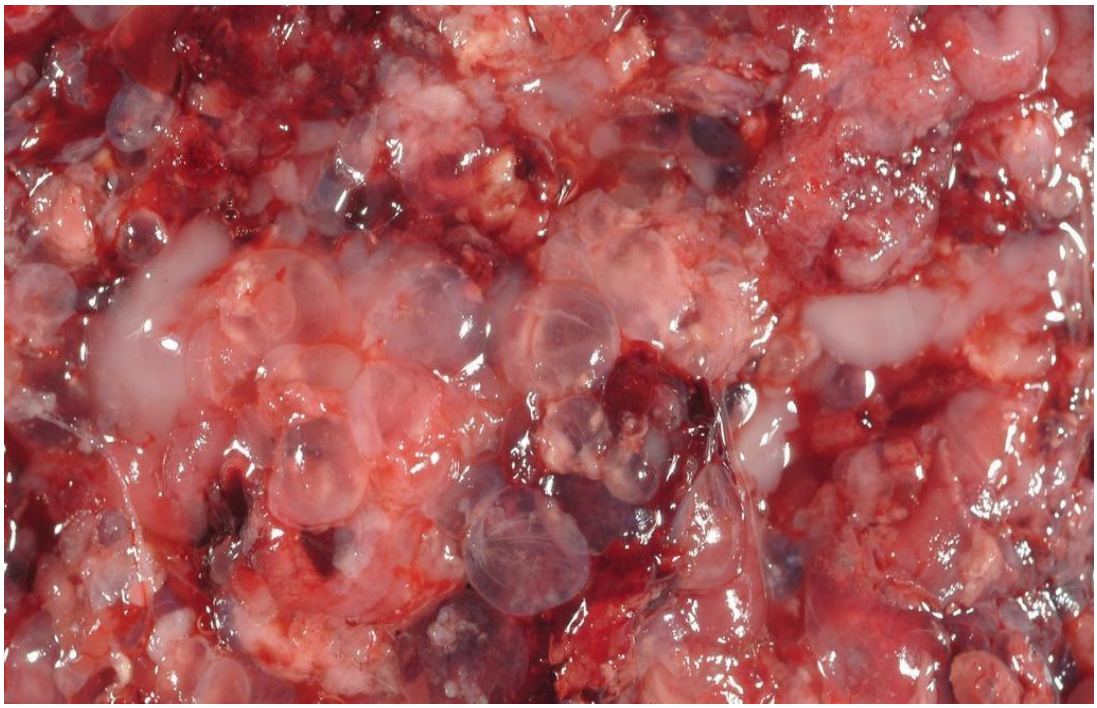
Molar pregnancies are subdivided into complete mole (CM) and partial mole (PM) based on cytogenetic, histopathological and clinical features.

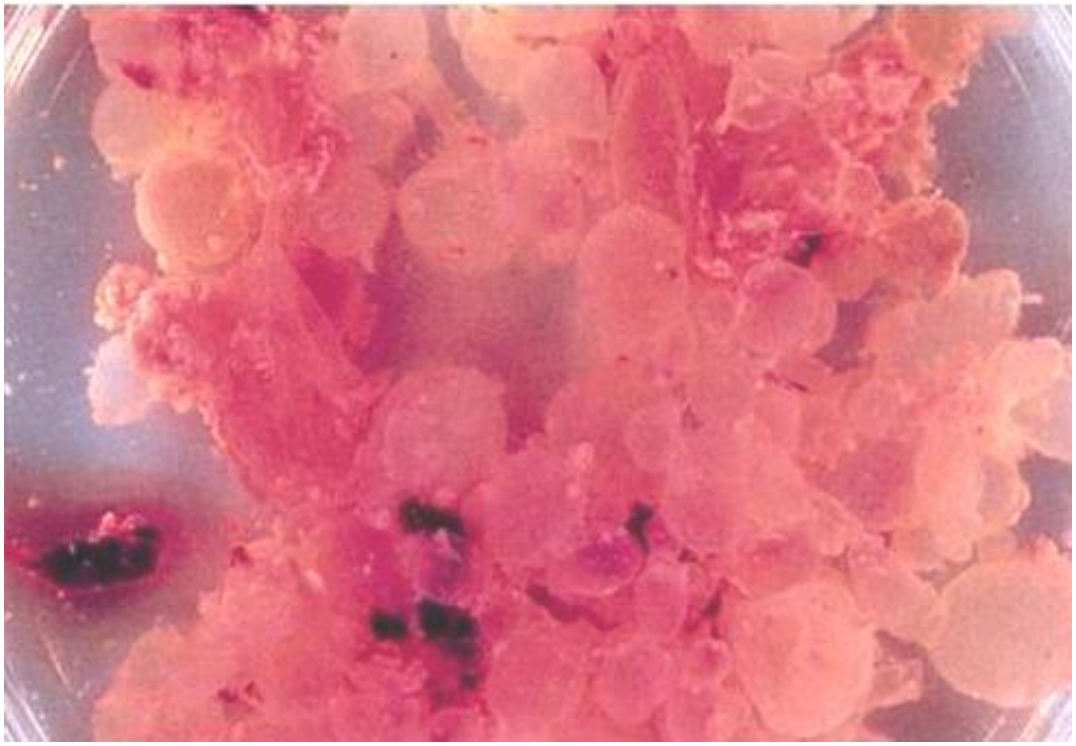
CM are diploid and androgenic in origin .CM arise as a consequence of duplication of a single sperm following fertilization of an empty ovum (75-80%) or dispermic fertilization of an empty ovum (20-25%).

PM are usually triploid (90%) in origin by dispermic fertilization of ovum. 10% of PM are tetraploid or mosaic conceptions.

Morphological distinction of non-molar miscarriage from partial hydatidiform mole can be difficult. P57kip2 is expressed by the maternal allele and is visible on histology as nuclear staining of cytotrophoblast of all gestations apart from androgenetic complete mole. Additionally, ploidy analysis by flow cytometry can distinguish diploid from triploid conceptions, helping to diagnose partial mole.

Figure - 1
Gross photograph of hydatidiform mole





CLINICOPATHOLOGIC FEATURES OF

GESTATIONAL TROPHOBLASTIC DISEASE

GTD	Pathologic features	Clinical features
Hydatidiform mole, Complete	46,XX (mainly); 46,XY Absent fetus/embryo Diffuse swelling of villi Diffuse trophoblastic hyperplasia	15-20% trophoblastic sequelae β hCG often >100,000 mIU/mL Medical complications common
Hydatidiform mole, partial	Triploid (69, XXY; 69, XYY; 69 XXX) Abnormal fetus/embryo Focal swelling of villi/trophoblast inclusions Focal trophoblastic hyperplasia/scalloping of villi	<5% trophoblastic sequelae βhCG usually<100,000mIU/mL Rare medical complications
Invasive Mole	Myometrial invasion Swollen villi Hyperplastic trophoblast	15% metastatic to lung/vagina Most often diagnosed clinically, rather than pathologically
Choriocarcinoma	Abnormal trophoblastic hyperplasia and anaplasia Absent villi Hemorrhage, necrosis	Vascular spread to distant sites–lung/brain/liver Malignant disease
PSTT	Tumor cells infiltrate myometrium with vascular/lymphatic invasion Intermediate cells present Absent villi Less hemorrhage and necrosis,Tumor cells stain positive for hPL	Extremely rare β hCG levels less reliable indicator Relatively chemoresistant Mainly surgical treatment

Figure - 2
Photomicrograph of complete hydatidiform mole demonstrating a markedly edematous villus with central cisternae formation

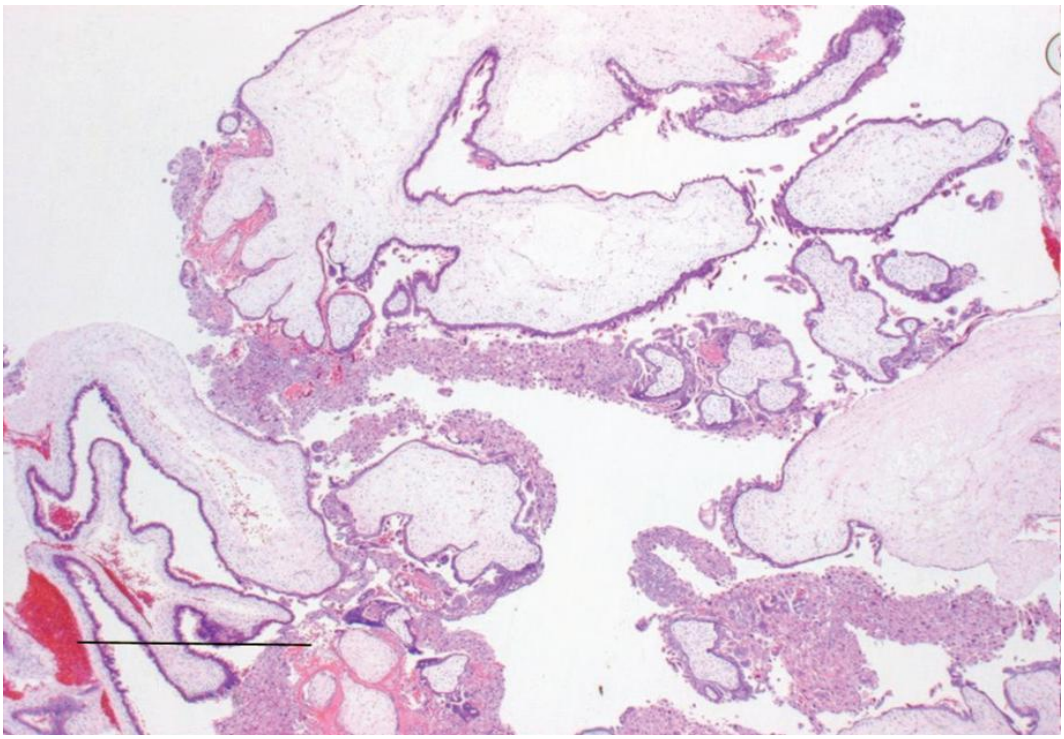
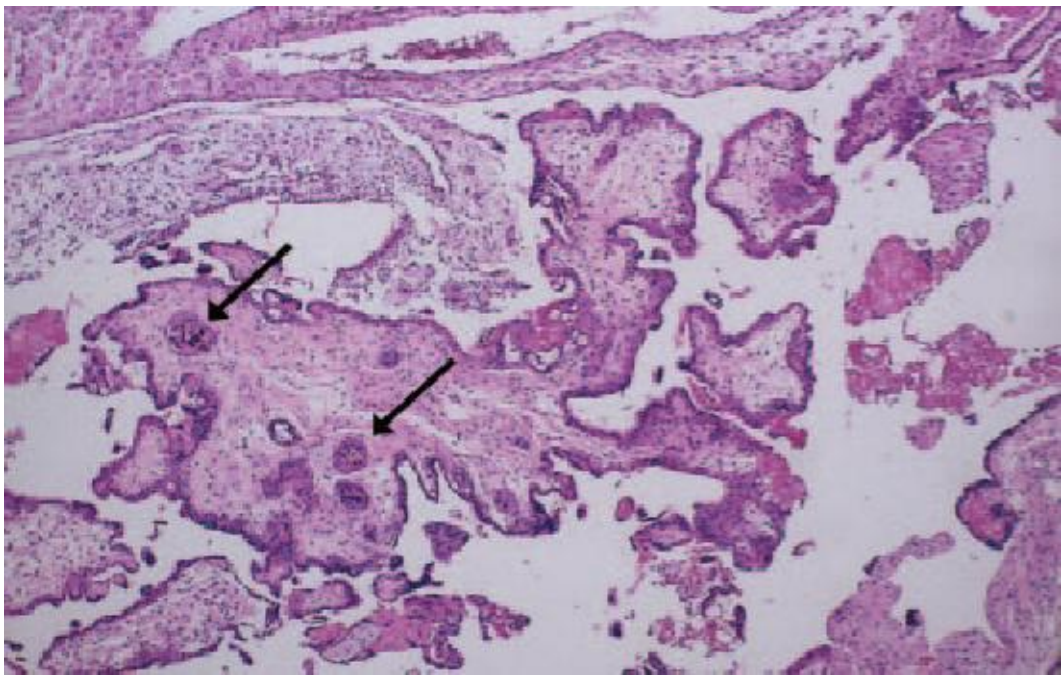


Figure - 3
Photomicrograph of a partial mole



Approximately 10-17% of hydatidiform mole will result in invasive mole which arises from myometrial invasion of a hydatidiform mole via direct extension through tissue or venous channels. Invasive mole is characterized by the presence of edematous chorionic villi while choriocarcinoma lacks villi formation.

Placental-site trophoblastic tumors grow more slowly; can arise after any type of pregnancy. Histological analysis is needed to substantiate the diagnosis.

Placental-site trophoblastic tumours, represents 0·2% of gestational trophoblastic diseases and arise from intermediate trophoblast of the placental implantation site.

Epithelioid Trophoblastic Tumor – ETTs are the most recently described and rarest of trophoblastic tumors. It is composed of chorionic type intermediate trophoblast and is distinct from both CC and PSTT with distinctive hyalinization. Most ETTs present many years after a full-term delivery.

ETT usually presents as a discrete uterine mass and stains diffusely positive with PLAP (placental specific alkaline phosphatase), cytokeratin, p63 and inhibin α whereas β hCG and hPL positivity is weak and scattered.

Figure - 4
Invasive mole with direct extension of molar tissue, including hydropic villi and covering hyperplastic trophoblast, into the myometrium

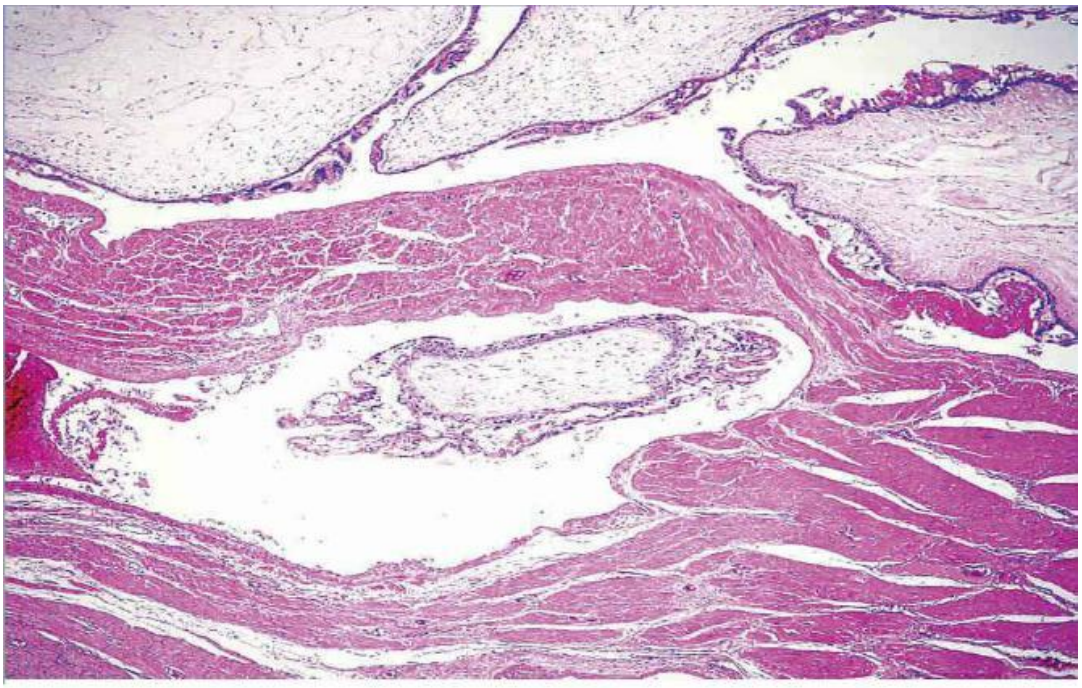
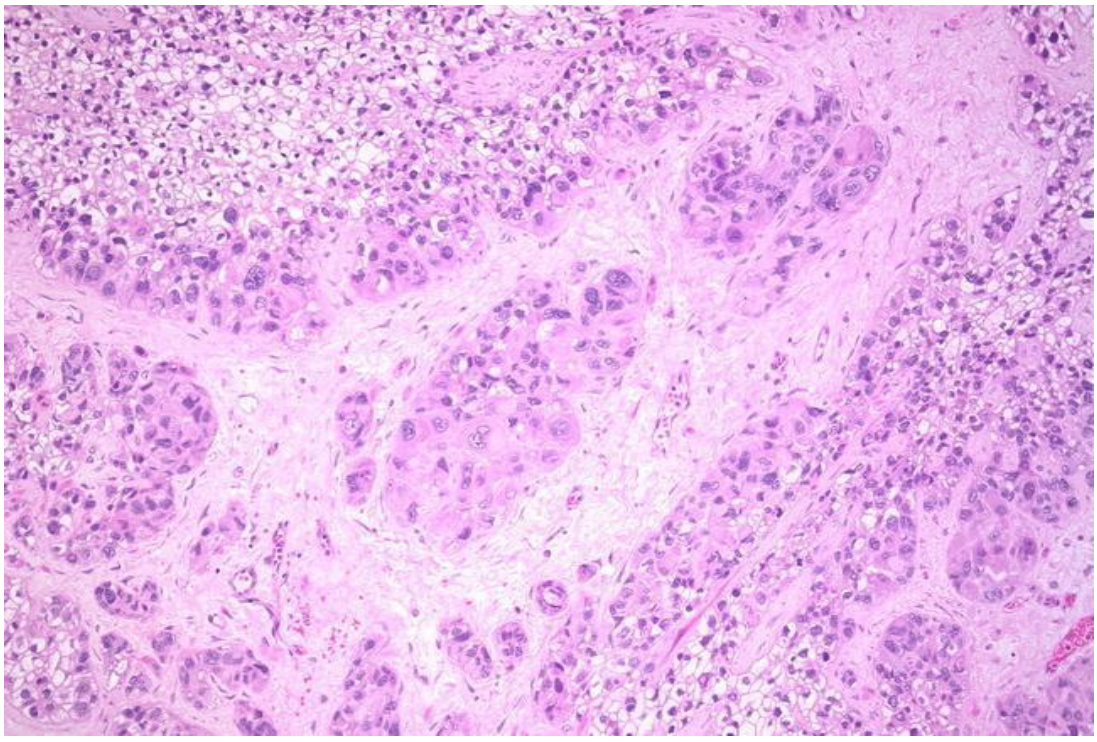


Figure - 5
Photomicrograph of epithelioid trophoblastic tumor



ETT is truly a rare but distinct trophoblastic tumor rather than just a morphological variant of PSTT, although the biological behavior appears similar .In contrast to placental site trophoblastic tumor, the cells of ETT are smaller and display less nuclear pleomorphism. In addition, ETT grows in a nodular fashion compared with the infiltrative pattern of placental site trophoblastic tumor.

MOLECULAR PATHOGENESIS

Genomic imprinting is believed to play a pivotal role in the pathogenesis of hydatidiform mole. Similar to other human cancers, malignant transformation in gestational trophoblastic tumors is likely a multistep process and involves multiple genetic alterations including activation of oncogenes and inactivation of tumor suppressor genes.

In addition, expression of telomerase activity, altered expression of cell-cell adhesion molecules and abnormal expression of matrix metalloproteinase have also been reported for in the pathogenesis of malignant transformation of GTD. These represent disruption of the delicate balance and regulation of cellular processes including proliferation, differentiation, apoptosis and invasion.

In complete mole, strong expression of epidermal growth factor receptor (EGFR) and c-erbB3 in the extra villous trophoblasts was significantly associated with the development of post molar tumor.

Marked down regulation of heat shock protein 27 in gestational trophoblastic tumors contributes to the marked sensitivity of the tumor to chemotherapy.

HUMAN CHORIONIC GONADOTROPHIN (HCG)

hCG is a disease-specific tumor marker produced by hydatidiform mole and gestational trophoblastic neoplasms.

It is easily measured quantitatively in both urine and blood, and hCG levels have been shown to correlate with the burden of the disease.

It is a placental glycoprotein composed of 2 dissimilar subunits: an α subunit of 92 amino acids resembling that of the pituitary glycoprotein hormones and a β subunit of 145 amino acids that is unique to placental production.

Although accurate measurements of β hCG levels are invaluable in diagnosing and later monitoring GTD, some laboratory assays may yield false-positive β hCG results.

These so-called **phantom hCG** with levels reported as high as 800 mIU/mL, have led to treatment of healthy patients with unnecessary surgery and chemotherapy.

The heterophile (human antimouse) antibodies are found in 3-4% of healthy people and can mimic β hCG immunoreactivity

There are 3 ways to determine whether hCG assays are falsely positive when there is a clinical suspicion of phantom hCG:

(1) Determine urine hCG level, which should be negative because the interfering substances are not excreted in urine;

(2) Request serial dilution of the serum, which should not show a parallel decrease with dilution; and

(3) Send the serum and urine of the patient to an hCG reference laboratory.

Additionally, there is some cross-reactivity of β hCG with luteinizing hormone (LH), which may lead to falsely elevated low levels of β hCG.

Measurement of LH to identify this possibility and suppression of LH with oral contraceptive pills will prevent this problem.

"**Quiescent gestational trophoblastic disease**" is a term applied to a presumed inactive form of GTD that is characterized by persistent, unchanging low levels (200 mIU/mL) of "real" β hCG for at least 3 months associated with a history of GTD or spontaneous abortion, but without clinically detectable disease. The β hCG levels do not change with chemotherapy or surgery. Follow-up of patients with presumed quiescent GTD reveals subsequent development of active GTN in about one-quarter.

According to the International Society for the Study of Trophoblastic Diseases 2001 recommendations

1. False-positive β hCG resulting from heterophile antibodies or LH interference should be excluded.

2. The patient should be thoroughly investigated for evidence of disease, immediate chemotherapy or surgery should be avoided.

3. The patient should be monitored long term with periodic β hCG testing while avoiding pregnancy.

4. Treatment should be undertaken only when there is a sustained rise in β hCG (3000mIU/ml) or the appearance of overt clinical disease.

5. To exclude pituitary hCG which is mostly found in older peri menopausal women, and is completely benign and can be resolved using hormone replacement therapy for 3 weeks.

DIAGNOSIS OF GTN

FIGO standardized the criteria used for the diagnosis of GTN (Ngan HY et al)

1. β hCG levels plateau plus or minus 10% of baseline recorded over a period of three consecutive weeks (1,7,14,21 days).

2. β hCG levels rise greater than 10% of baseline recorded over a period of two consecutive weeks (days 1,7,14).

3. Persistence of detectable β hCG for more than 6 months after molar evacuation.

4. Histological evidence of choriocarcinoma.

WORK UP OF PATIENT WITH GTN

Women newly diagnosed with GTN require a thorough evaluation of the extent of their disease such that the appropriate treatment can be selected.

This evaluation includes a history and physical examination, serum quantitative βhCG level, a complete blood count, and hepatic and renal function tests.

A pelvic ultrasound is often useful to detect the extent of uterine involvement and may identify patients who are at risk for uterine perforation or who would benefit from a hysterectomy to reduce tumor burden.

A chest X-ray should be obtained to evaluate lung metastasis. If this is negative, and lung metastasis suspected in symptomatic patients, chest computed tomography (CT) scan may be performed since it may detect micro metastases in 40% of patients with a negative chest X-ray.

Additional imaging can be omitted in patients with a negative chest CT given that distant metastases are unlikely in the absence of lung metastases.

Conversely, abdominal and brain imaging are an essential part of the workup in patients with metastases to the vagina or to the lungs and in patients with a histological diagnosis of choriocarcinoma.

Furthermore, an elevated cerebral spinal fluid/plasma β hCG ratio may suggest cerebral involvement. Additional imaging, such as FDG-PET scan, may be useful to accurately outline sites of metabolically active metastases and help determine the potential for tumor resectability.

REVISED FIGO 2000 RISK SCORING AND ANATOMIC STAGING

Bagshawe first introduced risk scoring in 1974 for malignant trophoblastic disease. Since 2002, all physicians treating gestational trophoblastic neoplasia should use FIGO system to allow comparison of data.

The combined prognostic score predicts potential for development of resistance to mono chemotherapy with methotrexate or actinomycinD.

A score of 0–6 suggests low risk of resistance and 7 or more indicates high risk of resistance to chemotherapy. Low risk GTN cases are treated with single agent chemotherapy. High risk disease has almost no chance of being cured with mono chemotherapy and needs multidrug treatment.

Anatomical staging does not aid therapeutic choices but helps clinicians to compare results between centers.

Patients should have doppler pelvic ultrasonography to measure the uterine tumor size and volume, local spread of disease within the pelvis, and disease vascularity. Disease vascularity can suggest patients who are at risk of treatment resistance.

Figure - 9
Chest X ray showing pulmonary metastasis in GTN

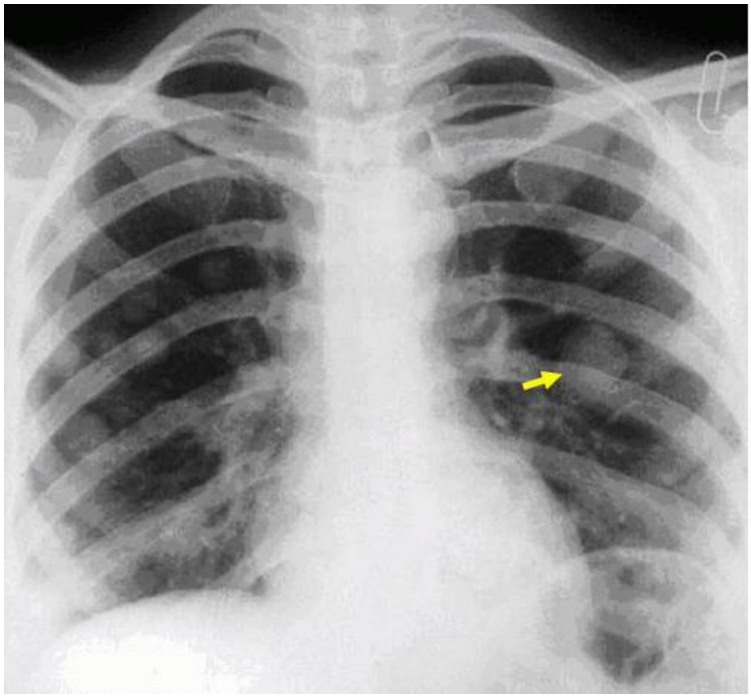


Figure -10
Doppler ultrasound examination of a complete hydatidiform mole with a vascular uterine mass

FIGO ANATOMIC STAGING FOR GTN

Stage 1 - Disease is confined to uterus

Stage 2 - Disease extends to the genital tract

Stage3 – Disease spread to lungs with or without extension to the genital tract

Stage 4 - Disease spread to all other metastatic sites like brain, kidneys and liver

International Federation of Gynecology and Obstetrics (2000)

Scoring System for Gestational trophoblastic neoplasia by prognostic factors

	0	**1**	**2**	**4**
Age(years)	<40	>40		
Antecedent pregnancy	Mole	Abortion	Term pregnancy	
Interval from antecedent pregnancy to chemotherapy (months)	<4	4-6	7-12	>12
β hCG concentration (IU/L)	$<10^3$	$10^3 – 10^4$	$10^4 – 10^5$	$>10^5$
Number of metastasis	0	1-4	5-8	>8
Site of metastasis	Lung	Spleen, Kidney	Gastro intestinal tract	Liver, Brain
Largest tumor mass diameter (cms)	-	3-5	>5	-
Previous Chemotherapy	-	-	Mono therapy	Combined therapy

Gestational trophoblastic diseases are tumor and tumor like condition that originate from the fetal chorion. Trophoblastic tumors are fetal allograft in maternal tissues and present unique biological, immunological and pathological problems.

INCIDENCE

The reported incidences of hydatidiform mole vary widely in different regions of the world.

Incidences are highest in South East Asia, Indonesia, India and Turkey with rates ranging from 2 to 12 per 1000 pregnancies[6].

Estimates from studies in North America, New Zealand and Australia have shown the incidence to range from 0.57 to 1.1 per 1000 pregnancies[7].

In UK, the incidence of GTD is 1 in 714 live births.[1]

A hospital based study by Tham BW et al from England and North Wales shows the women of Asian descent have two to three fold higher rates of hydatidiform mole compared with non Asian women (1/387 vs1/752). [16]

The high incidence in certain population has been attributed to socio economic and nutritional factors and not due to genetic traits and cultural factors (John RL et al) [7].

REVIEW OF LITERATURE

Patient score is a total of individual scores of the eight prognostic factors**.** PSTT should not be scored but needs to be staged.

COEXISTENT MOLE AND FETUS

Coexistence of a fetus with molar change of the placenta is relatively rare, occurring in 1 of 22,000–100,000 pregnancies.

Medical complications of hydatidiform mole appear to be increased. Studies show that compared with singleton hydatidiform mole, twin pregnancies with fetus and mole has increased risk for post molar GTN.

Major congenital abnormalities have not been reported in surviving infants. Prenatal invasive testing for fetal karyotype should be considered in cases where it is unclear if the pregnancy is a complete mole with a coexisting normal twin or a partial mole.

The outcome for a normal pregnancy with a coexisting complete mole is poor, with approximately a 25% chance of achieving a live birth.

There is an increased risk of early fetal loss (40%) and premature delivery (36%).

The incidence of pre-eclampsia is variable, with rates as high as 20% reported.

As per a study by Kim SJ et al from Korea, the hospital based incidence of molar pregnancies has declined from 40 per 1000 deliveries during 1970s to 2 per 1000 deliveries during 1990s[17].

The reduction in incidence is due to increased socioeconomic_status, changes in diet and maternal age at child birth, fall in birth rates, changes in diagnostic accuracy, and reporting variations (Berkowitz RS et al). [9]

AGE

Advanced or very young maternal age has consistently been correlated with higher rates of complete mole (Lybol C et al 2011).[18]

Compared to women aged 21 to 35 years, the risk of complete mole is 1.9 times higher in women more than 35 years and less than 21 years of age and is 7.5 times higher in women greater than 40 years of age (Sebire NJ et al).[19]Abnormal fertilizations are common in ova from women of extremes of age.

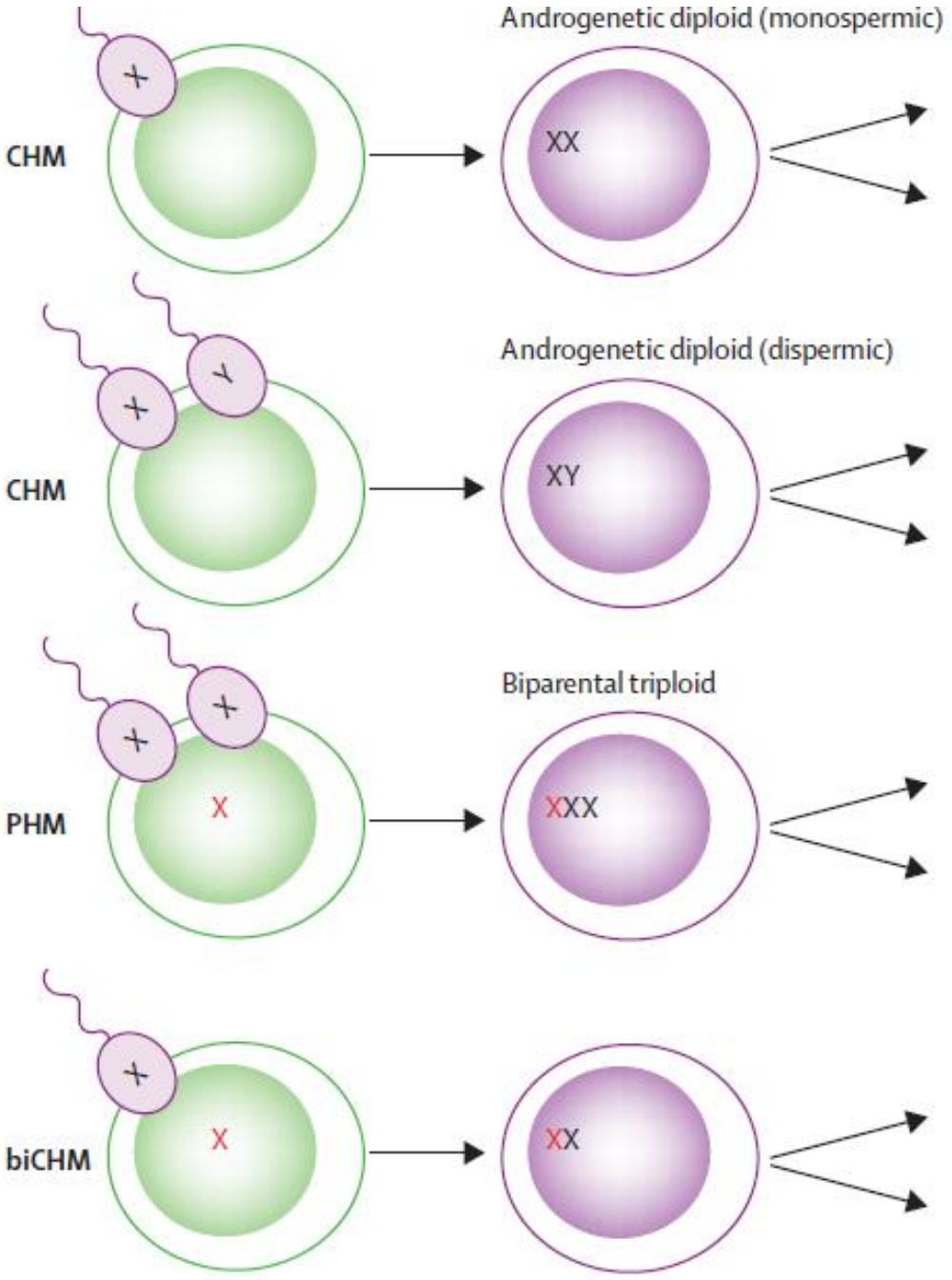
In a study by Kumar N et al, major risk factor for complete mole is age more than 30 years (RR 3.9).[20]

In women over the age of 50 years one out of three pregnancies are molar (Berkowitz RS) [9].

Age is less likely to be a factor for partial mole (Parazzini et al) [22].

Figure - 8

Karyotype derivation of complete and partial hydatidiform mole and rare biparental repetitive complete hydatidiform mole.



Another obstetric risk factor for complete and partial mole is a history of spontaneous abortion. There is a 2 to 3 fold increased risk of molar pregnancy in women with a history of spontaneous miscarriage (Parazinni F et al) [22].

Difficulty in conception and infertility problems are associated with odds risk of 2.4 and 3.2 respectively for complete and partial mole (Berkowitz RS) [9].

Among the environmental factors, only consistent association has been an inverse relationship between beta carotene and animal fat dietary intake and the incidence of complete molar pregnancies. Diet can reset the genetic imprint (Lurain JR et al) [7].

Risk of partial mole appears to be associated with reproductive history like use of oral contraceptives and a history of irregular menstruation but not with dietary factors or maternal age (Berkowitz RS et al) [26].

The risk of gestational trophoblastic neoplasia is related to hormonal factors and is increased in women with light menstrual flow and menarche after the age of 12 years (Berkowitz RS et al).[9]

CLINICAL FEATURES

In recent years, the availability of ultrasound and sensitive β hCG tests has meant a change in the clinical presentation to earlier detection at a gestational age of 10–12 weeks (Nienke EVT et al) [6].

In UK, greatest number of GTD cases (80%) occurred between the ages of 20 to 39 years (Pisal N et al) [2].

In a study from All India Institute of Medical Sciences, New Delhi by Hari Prasad R et al, the mean age of presentation of GTD was 28.2 years[21].

RISK FACTORS

Prior hydatdiform mole predisposes to another molar pregnancy. The risk of repeat molar pregnancy after one mole is about 1% or about 10 to 20 times the risk of general population (Berkowitz RS) [9].

After two molar gestations the risk of third mole is 15 to 20 % (Garett LA et al) [23].

Recurrent molar pregnancies are autosomal recessive condition with biparental diploid chromosomes and have significant under expression of p52 (KIP2) which has important role in apoptosis and tumor expression (Fisher RA et al) [24]. Risk is not decreased by change in partner.

Familial clusters of biparental repeat complete mole are associated with novel missense NLRP7 gene mutation on chromosome 19q13.3-13.4.

The function of the normal protein and the mechanism by which mutations are associated with imprinting abnormalities are not known (Fisher RA et al) [24].

Respiratory distress caused by trophoblastic embolisation is rare and observed around the time of molar evacuation among patients with uterine enlargement greater than 14 to 16 weeks size (John T S et al) [4].

With routine first trimester ultrasonography, a significant proportion of patients (41%) are asymptomatic at the time of diagnosis (Johns J et al) [29] and may present sonographically as early pregnancy failure or anembryonic pregnancy. This highlights the importance of histological examination of the products of conception of anembryonic pregnancies (Fowler DJ et al) [30].

Estimation of β hCG values may be of value in diagnosing molar pregnancies (β hCG greater than 2 multiples of median).

Partial mole present with symptoms of missed or incomplete abortion like vaginal bleeding (75%) and are usually diagnosed by histological review of curettage specimen (Berkowitz RS) [9].

A urine pregnancy test should be performed in all cases of persistent or irregular vaginal bleeding after a pregnancy event.

Symptoms of metastatic disease such as dyspnoea, hemoptysis, chest pain, headache, seizures, hemiparesis can occur very rarely (RCOG GTG 38)[1].

The prognosis of women with GTN after a non molar pregnancy is worse due to delay in diagnosis or advanced disease at presentation (RCOG GTG 38)[1].

The classic clinical features of molar pregnancy are irregular vaginal bleeding, vomiting, excessive uterine enlargement, and early failed pregnancy (RCOG GTG 38)[1].

Vaginal bleeding is the most common presenting symptom in patients with complete mole occurring in 80 to 90% of cases.

Currently anemia is present in only 5%of cases due to occult bleeding. Vomiting requiring antiemetic therapy is present in 8% of patients due to high β hCG values (Savage P et al) [8].

Uterine enlargement greater than the expected dates is present in 28% of patients and is due to retained blood and trophoblastic proliferation.

Pre eclampsia occurs less frequently (1%) because of earlier diagnosis. (Gemer O Segal et al) [27].

7% patients with GTD had biochemical hyperthyroidism and 2% had clinical hyperthyroidism (Walkington et al) [28].

Bilateral theca leutin cyst enlargement of the ovaries occurs in approximately 15% of cases. (β hCG levels> one lakh IU/ml). The resolution of theca leutin cysts lags behind the drop of β hCG and may take several months to resolve after molar evacuation but rarely require surgical intervention for torsion or rupture (Hou JL et al)[31].

DIAGNOSIS

The routine use of ultrasound in early pregnancy has probably led to the earlier diagnosis of molar pregnancies. The accuracy of ultrasound diagnosis of molar pregnancy is increased with increasing gestational age, 35 to 40% before 14 weeks to 60% after 14 weeks (Fowler DJ et al).[30]

The ultrasound finding of cystic spaces in the placenta and a ratio of transverse to anteroposterior dimension of gestational sac greater than 1.5 has a positive predictive value of 87% in the diagnosis of partial mole (Finc C et al) [32].

In the second trimester, complete mole is recognized in ultrasound as numerous vesicular structures filling the uterine cavity often with a snow storm appearance.

Patients with molar pregnancies have markedly elevated pre evacuation β hCG values

In GTD, several forms of hCG (6 major variants) exist, free β hCG, free α hCG, hypergycosylated hCG , β core hCG, nicked free β hCG, absent C terminal peptide (Cole LA et al) [33].

In the UK, non commercial rabbit polyclonal antibody that detects all forms of β hCG with low false negative rate is used. The only commercial assay that is comparably safe is Siemens Immulite (Deerfield, IL, USA) (Cole LA et al) [34].

Figure - 13

Pelvic ultrasound of complete hydatidiform mole with characteristic vesicular pattern of multiple echoes

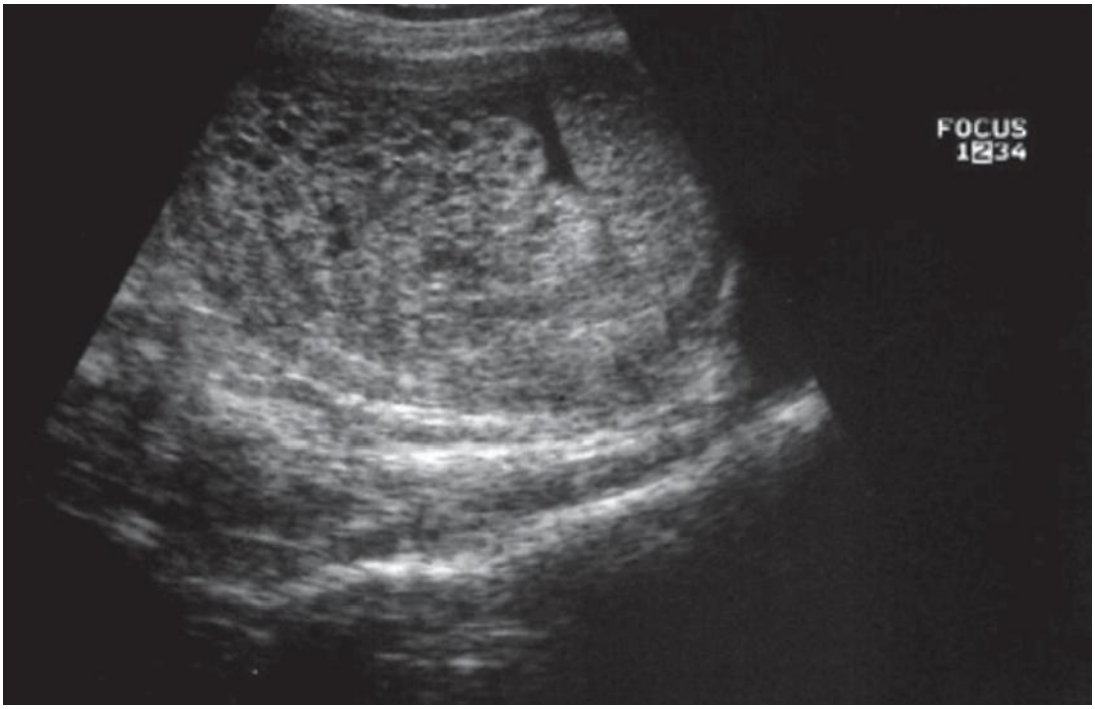
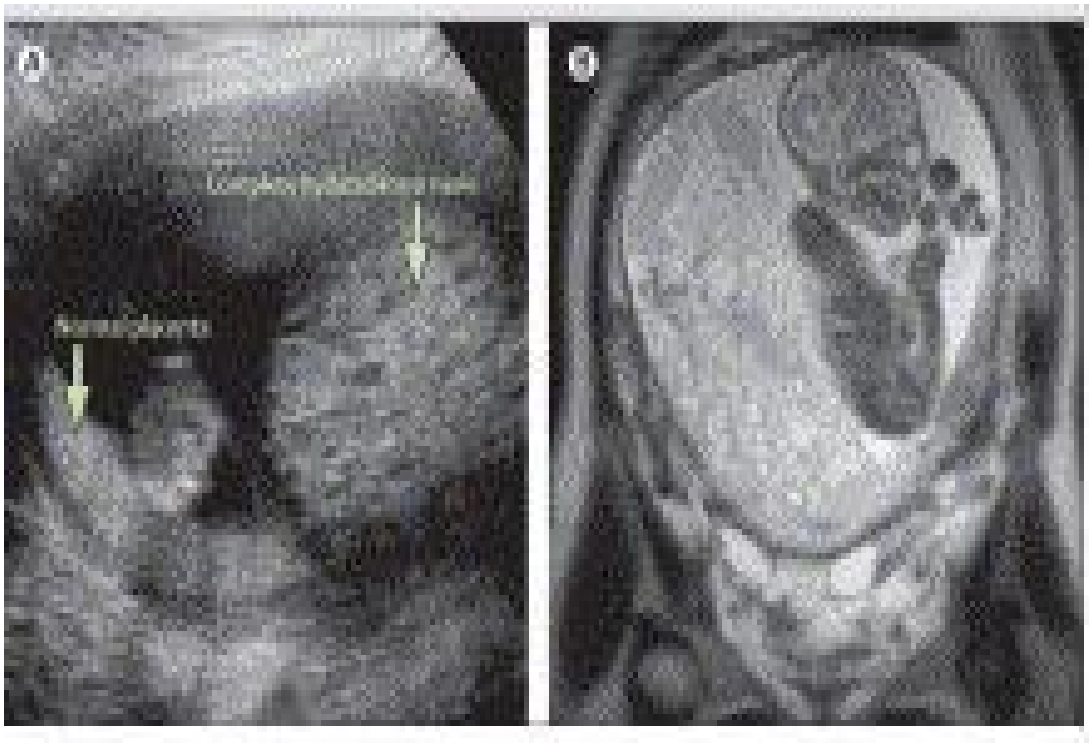


Figure 14

Ultrasound and MRI of a complete hydatidiform mole and healthy co-twin



High rates of hyperglycosylated hCG variant to total hCG can detect malignant forms of GTD (Cole LA et al) [34].

Free β hCG is a marker for PSTT (Harvey RA et al) [35].

SURGICAL EVACUATION

Suction curettage is the method of choice of evacuation for molar pregnancies. When the size of fetal parts deters the use of suction curettage in partial mole, medical evacuation can be used.

Anti D prophylaxis is required following evacuation of molar pregnancy in Rh negative women (RCOG GTG 38)[1].

Medical evacuation of complete mole should be avoided if possible (Tidy J et al) [36].

Hysterectomy is rarely recommended but might be considered for women who have completed families, or have life threatening hemorrhage or sepsis or in stage1 PSTT (Elias K et al) [37].

Although hysterectomy stops the risk of local invasion, it does not eliminate the risk of GTN (3 -5%) and β hCG monitoring should still be done (Lurain JR et al) [7].

Preparation of cervix with prostaglandins immediately prior to evacuation is safe. Prolonged cervical preparation with prostaglandins is avoided to reduce the risk of trophoblast embolisation (RCOG GTG 38)[1].

Figure – 11
Serum ß-hCG following uterine evacuation[12]

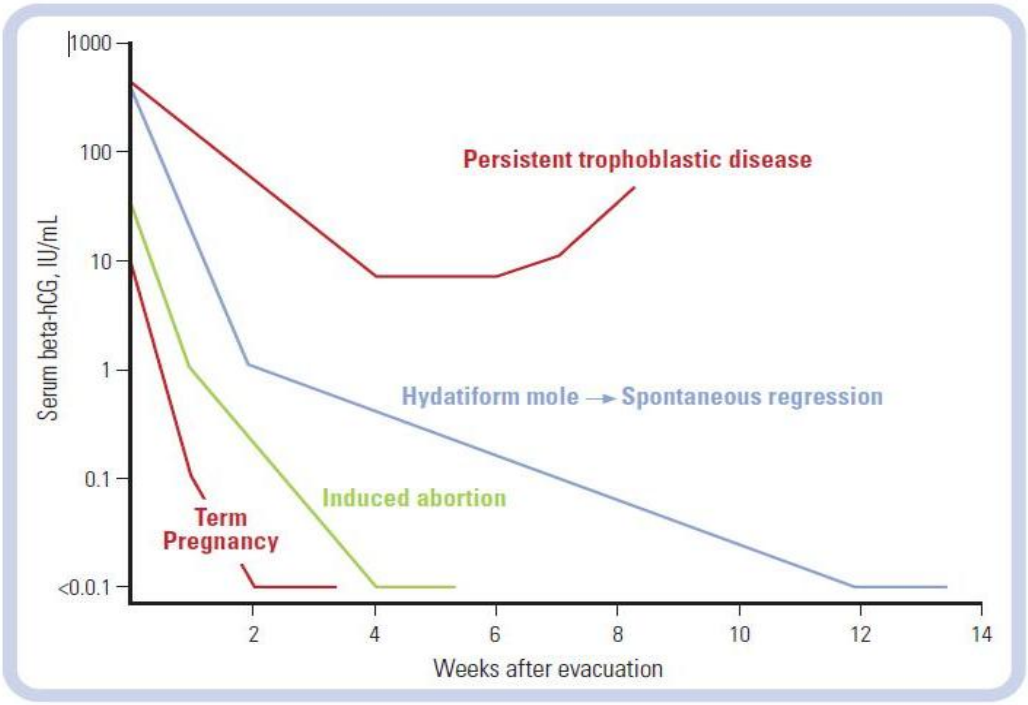
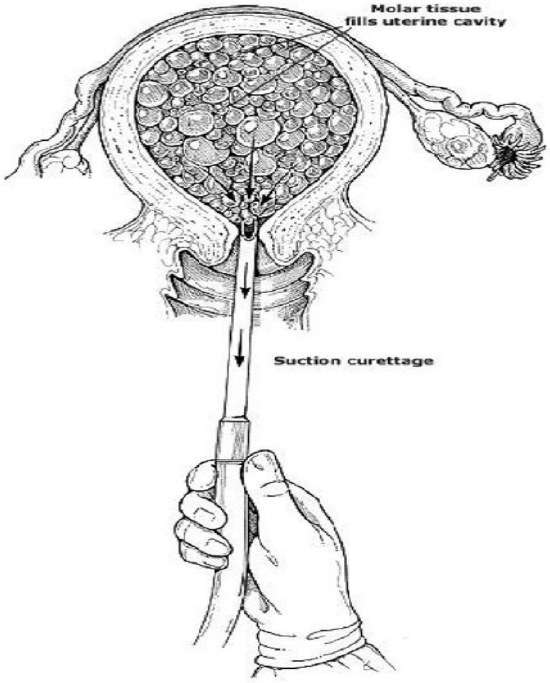


Figure - 12
Suction curettage of molar pregnancy[12]



The use of oxytocin infusion prior to the completion of evacuation is not recommended in view of trophoblast embolisation.

In the presence of significant hemorrhage, the need for oxytocin infusion weighed up against the risk of embolisation of trophoblast cells (RCOG GTG 38)[1].

The histological examination of material obtained from the medical or surgical evacuation of all early failed pregnancies is recommended to exclude GTD (Well M et al) [38].

A urine pregnancy test should be performed 3 weeks after medical management of early failed pregnancy if products of conception are not sent for histological examination (Seckl MJ et al) [39].

There is no need to routinely send products of conception for histological examination following therapeutic termination of pregnancy provided fetal parts have been identified on prior ultrasound examination (RCOG GTG 38)[1].

There may be a role for second evacuation in persisting vaginal bleeding after molar evacuation in selected cases after ultrasound examination and β hCG values less than 5000 U/li **(**Pezeshki M et al) [41].

Consultation with a specialized center for treating GTD is recommended prior to second evacuation.

Biopsy of a vaginal lesion suggestive of a gestational trophoblastic tumor is dangerous because of the massive bleeding that may occur (Berry E et al) [40].

POST MOLAR SURVEILLANCE

Serial quantitative serum β hCG determinations should be done after molar evacuations using standard assays (<5mIU/ml) every 1-2 weeks till it becomes not detectable, then every 1-2 months for an additional 6-12 months (ACOG practice bulletin no. 53, 2004) [11].

If β hCG has reverted back to normal within 56 days of pregnancy event, then follow up will be for 6 months from the date of uterine evacuation.

If β hCG has not reverted back to normal, within 56 days of pregnancy event, then follow up will be for 6 months from the normalization of β hCG levels (Sebire NJ et al) [42].

Normalisation of serum β hCG after molar evacuation is within 6 weeks in 5% of patients and within 11 weeks in 50% of patients and within 25 weeks in 95% of patients (Yedema KA et al) [43].

PROPHYLACTIC CHEMOTHERAPY

Prophylactic Chemotherapy at the time of or immediately after molar evacuation is associated with reduction in incidence of GTN from 15 -20% to 3-8%.

The use of prophylactic chemotherapy is limited to special situations like high risk cases where follow up is not possible.

It can cause chemo resistance and adverse side effects and it does not completely eliminate the need for follow up.

Treating many patients to prevent a few GTN does not offer significant advantages over post evacuation follow-up (Limpongsanurak S et al) [44].

The low morbidity and mortality achieved by monitoring patients with serial β hCG determinations and instituting chemotherapy only in patients with post molar gestational trophoblastic disease outweighs the potential risk and small benefit of routine prophylactic chemotherapy (John TS et al) [4].

CONTRACEPTION

Women should be advised not to conceive until their follow up is complete. Two randomized control trials from NETDC and GOG shows oral contraceptive pills (OCPs) does not increase the risk of GTN (Costa HLF et al 2006) [45].

The conflicting data from a case series in UK showing increased risk of GTN in OCP users before β hCG levels are normal is explained by the higher dose of estrogen (> 50 micrograms) in OCPs (Stone M et al 1979)[46].

OCPs are preferable because they have the advantage of suppressing endogenous LH which may interfere with β hCG measurements.

OCPs are safe for use during the entire period of follow up (Gerulath A H et al) [10]. Intrauterine contraceptive devices should not be used because of the risk of uterine perforation.

RISK OF GTN

The likelihood of GTN is increased to 40% with pre evacuation β hCG more than a lakh mIU/ml, uterine size more than 20 weeks, theca luetin cysts more than 6 centimeters in diameter compared to 4% without any of these signs.

Patients more than 40 years, repeat molar pregnancy, heterozygous complete mole, aneuploid mole, mole with medical complications like preeclampsia, hyperthyroidism and trophoblastic embolisation are at increased risk of GTN (Berkowitz RS) [47].

The use of a normal uneventful β hCG regression corridor (>95th percentile) together with FIGO criteria for diagnosis of GTN facilitates early diagnosis (2 weeks before) and more expectant management of GTN (Behtah N et al) [48].

CHEMOTHERAPY

The landmark publication of Li et al in 1956, describes the success of methotrexate in treating gestational trophoblastic neoplasia.

Bagshawe and his associates first used EMA-CO in 1984 to treat malignant trophoblastic disease.

Indications for chemotherapy in UK include FIGO criteria for GTN, heavy vaginal or gastrointestinal or intraperitoneal bleeding, metastasis more than 2 centimeters diameter in the lungs and vagina, β hCG more than 20,000 one month after evacuation (Seckl MJ et al) [5].

For most **low risk GTN** patients, monochemotherapy with methotrexate or actinomycin D is the preferred treatment (Alazzam M et al)[49].

The commonly used regimens are weekly intramuscular methotrexate 50mg and oral folinic acid 15 mg, 30 hours after methotrexate (or) methotrexate 50 mg intramuscularly every 48 hours alternating with oral calcium folinate 15 mg each 4 doses every 2 weeks.

Most patients are treated at home after a short stay in hospital to monitor for bleeding.

About 2% of women treated experience side effects like mouth ulcers or pleuritic and peritoneal pains from serosities and gastrointestinal disturbances.

If β hCG values have not fallen by at least 10% over a cycle of therapy, treatment should be changed to an alternative single-agent regimen. Patients who develop resistance to methotrexate can be switched to D-actinomycin if β hCG concentrations < 100IU/li or multidrug chemotherapy if β hCG> 100 IU/li (Seckl M et al)[5] .

Chemotherapy should be continued until β hCG is normal and for a further 6 weeks to eliminate residual disease or relapse (Growdon WB et al) [5].

Low risk GTN patients scoring 5-6 with increased vascularity in doppler or β hCG > 4 lac IU/li is unlikely to be cured by monotherapy, hence multidrug regimens should be given from the outset. Overall survival is 100% in low risk GTN (McGrath et al) [50].

For **high risk GTN cases**, EMA-CO regimen every 2 weeks is effective worldwide with predictable and manageable short term side effects (Bagshawe KD et al). [51]

EMA-CO regimen necessitates overnight stay every two weeks, causes reversible alopecia and myelosuppression (filgrastim helps maintain neutrophil count and avoids febrile neutropenic episodes).

Long term survival is 27% in liver metastasis, 70% in brain metastasis, and 10% in both site metastases.

Most of high risk metastatic cases presented late with widespread disease, most had not had a molar pregnancy, and most were not registered for follow up.

Chemotherapy is continued for 6 weeks after normal β hCG or 8 weeks if brain or liver metastasis is present.

In drug resistant cases EMA-EP regimen is used. If patient fails to respond to methotrexate containing regimens , paclitaxol containing regimens alternating TE/TP every 2 weeks or ifosfamide containing regimens VIP or ICE is used (Wang J et al). [52]

12.5% of high risk GTN cases will develop recurrence after initial remission (Soper JT et al) [4].

TREATMENT OF METASTASES

Cranial radiotherapy is given concurrently with the initiation of chemotherapy with or without intrathecal methotrexate to shrink brain metastasis and to minimize intracranial bleeding.

Craniotomy and resection of drug resistant solitary lesions is very rarely indicated who do not have metastatic disease elsewhere (Synman LC et al) [12].

Hepatic resection and/or selective embolisation of the hepatic arteries may help in liver metastasis to control bleeding or remove resistant tumor.

A solitary chemoresistant pulmonary nodule can be treated with thoracotomy and wedge resection after ruling out other systemic metastases.

Vaginal metastases can cause heavy bleeding which can be controlled by packing. Alternatively, embolisation of the vaginal branch of the hypogastric artery can be considered (Synman LC et al) [12].

PSTT

The stage, β hCG, mitotic index, and duration of more than 4 years from preceding pregnancy were prognostic for PSTT.

Only time from previous pregnancy to first treatment remained predictive of survival. This effect was not explained by differences in disease stage or β hCG concentrations, but might suggest a biological switch in tumors after this time.

Management of placental-site trophoblastic tumour differs from that for choriocarcinoma (Schmid P et al). [53]

Patients with metastatic disease need combination chemotherapy (eg, EP-EMA) until 8 weeks of normal β hCG concentrations are recorded.

Residual masses are removed surgically, including the uterus, which can contain microscopic disease with sampling of pelvic lymph nodes and ovarian conservation, unless the patient has a family history of ovarian cancer or is postmenopausal (Taymaa May et al)[14] .

The adjuvant therapy after hysterectomy is 8 weeks of EP-EMA or TE/TP when there are poor risk factors such as disease presentation beyond 4 years from the antecedent pregnancy.

Hysterectomy is the first line of treatment in women with Stage 1 PSTT and ETT (Taymaa May et al) [14].

POST CHEMOTHERAPY SEQUALAE AND FOLLOW UP

Nearly all side effects of chemotherapy are reversible. Pregnancy rate after chemotherapy is more than 83% (Woolas RP et al) [54]. Incidences of congenital malformations are not increased in babies (1.8%). The rate of still birth (18.6/1000 births) is elevated compared with normal population (RCOG GTG 38).[1]

Patients are advised not to become pregnant until 12 months after completion of chemotherapy to reduce teratogenicity and to avoid confusion between a new pregnancy and relapsed disease.

The age of menopause is advanced by one year in patients who receive monotherapy and by 3 years in patients if they receive multidrug therapy.

Women with high risk GTN treated with etoposide containing multi drug regimens are at increased risk of developing secondary cancers, if they survive more than 25 years after chemotherapy (Relative Risk (RR) 16.6 for AML, RR 4.6 for colon cancer, RR 5.79 for breast cancer, RR 3.4 for melanoma) (Rustin GJS et al) [55].

If etoposide containing multidrug chemotherapy is limited to less than 6 months, there is no increased risk of developing secondary cancers.

The patients are followed up for a period of one year in low risk GTN and 2 years after completion of chemotherapy in high risk GTN cases because of late recurrence

If patients become pregnant after a molar pregnancy, early ultrasound examination is done to ensure healthy pregnancy and to rule out repeat mole.

Serum β hCG is done at 6 weeks and 10 weeks at the end of any future pregnancy event after GTD to exclude disease recurrence. The pathologic examination of placentas and other products of conception are recommended in all future pregnancies.

A prospective study of Gestational trophoblastic disease from one of the largest tertiary referral center in Tamil Nadu ,The Institute of Obstetrics and Gynecology, Madras Medical College, Chennai, conducted over a period of one year (May 2010 to April 2011) covering 114 patients.

- Estimation of the incidence of molar pregnancies at IOG.
- Estimation of the incidence of post molar trophoblastic neoplasia among the molar pregnancies.
- Descriptive analysis of the epidemiological factors, natural history, treatment and outcome of GTD patients at IOG.

MATERIALS AND METHODS

- **Setting**

  Institute of Obstetrics and Gynecology, Egmore , Chennai – 600 008.

- **Collaborating Units**

  Department of Medical Oncology, IOG

  Department of Pathology, IOG

- **Design**

  Prospective longitudinal Descriptive Study

- **Statistical Analysis**

  Frequency distribution of variables and log value regression curve from the means and standard deviation of serial monthly β hCG values of uneventful molar pregnancies and GTN using SSPN.

- **Period**

  May 2010- April 2011

- **Study Population**

  All women with GTD attending IOG during May 2010-April 2011

INCLUSION CRITERIA

- Women admitted in IOG with complete mole, partial mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor.
- Women with persistent and malignant trophoblastic diseases referred to IOG for tertiary care.

METHODOLOGY

- Standardized protocols are followed for registration, assessment, treatment and follow up of patients with molar pregnancy attending IOG.
- After getting informed consent, women are interviewed, examined and registered as per standard clinical guidelines.
- A Record is maintained regarding information on
    1. History
    2. Physical examination
    3. Ultrasound
    4. Initial β hCG and subsequent values
    5. Chest x-ray
    6. Histological diagnosis
    7. Evacuation details

8. Pretreatment WHO Risk Score and
9. Details of Chemotherapy if given

- Suction evacuation is the procedure of choice.
- Patients are advised to use oral contraceptives after evacuation for the follow up period.
- At follow up, patients are examined clinically and serum β hCG is done at regular intervals, and imaging procedures are done if needed.
- In asymptomatic patients serial serum β hCG is measured once in 4 weeks and in symptomatic patients serial serum β hCG is done once in 2 weeks during follow up period.
- After β hCG value normalizes, patients are followed up for a period of 12 months in uneventful cases.
- Low risk GTN cases are followed up for a period of one year after completion of single agent chemotherapy.
- High risk GTN cases are followed up for a period of 2 years in GTN cases after completion of multi agent chemotherapy.
- In our study, we have followed up the patients till September 2011.
- The data collected are analyzed using statistical methods for the estimation of the incidence of molar pregnancies at IOG

- Epidemiological factors, natural history and follow up of molar pregnancies are descriptively analyzed.

- The incidence of persistent post molar trophoblastic diseases among molar pregnancies (high risk and low risk) and their response to chemotherapy (single and multiple agents), the dynamics of β hCG fall and the outcome of treated patients are studied.

OBSERVATION AND ANALYSIS

RESULTS

Total number of GTD cases	**114**
Cases at IOG	102
Referral cases	12

Referral cases

ISO-KGH	-3
RSRM	-1
Private hospitals	-6
Arakkonam GH	-1
KMC	-1
Total referral	**-12**

Cases at IOG (102)

Total GTD	**102**
Normal Molar pregnancies	90
Low risk GTN	12

This observational study is a hospital based study and not population based. During the study period there were a total of 20,275 pregnancies in the Hospital for Women and Children, Egmore, Chennai. The pregnancies include abortions both induced and spontaneous, live births, intrauterine deaths, spontaneous expulsions, still births, and ectopic pregnancies.

Total number of cases during the study period is 114 of which 12 cases were evacuated outside and referred for tertiary care.

102 cases of GTD were treated and followed up at IOG (chart -1).

Incidence of molar pregnancies is 5 per 1000 pregnancies at our institution.

Of the 102 cases, 12 cases were low risk GTN and 90 cases were benign molar pregnancies.

Total number of GTD cases at IOG -102

Complete mole	80	78.4%
Partial mole	21	20.6%

Of the total GTD cases at IOG, 78.4% were complete mole and 20.6% were partial mole (Chart 2).

Chart -1:

TOTAL GTD CASES -114

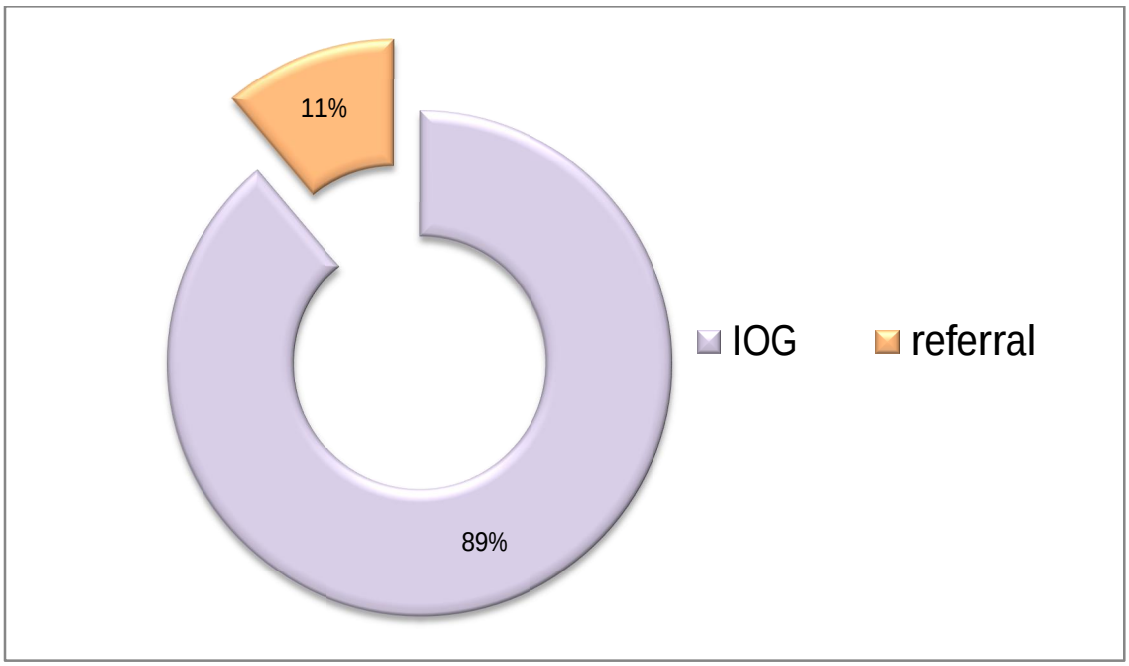
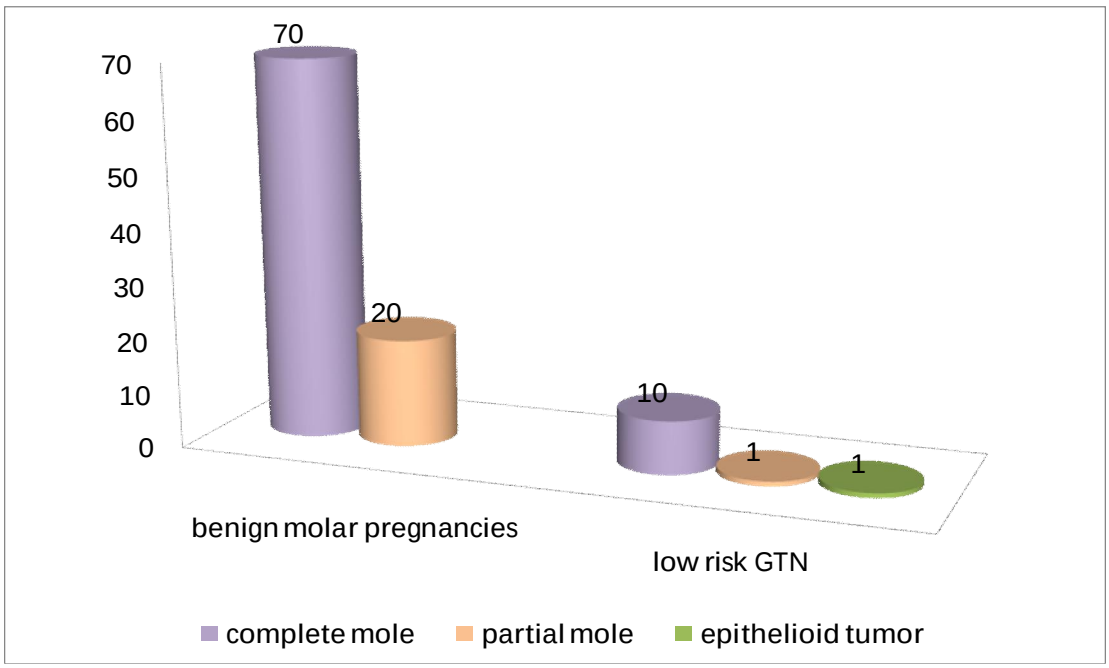


Chart -2:

CASES AT IOG (102 cases)



Of the 12 low risk GTN cases at IOG, 10 cases (83.4%) were following complete mole and one low risk GTN case (8.3%) was following partial mole.

Among the low risk GTN cases at IOG, there were 5 cases (41.6%) of invasive mole.

One case (8.3%) of epithelioid trophoblastic tumor presented 10 years after last child birth. There was no case of high risk disease at IOG.

REFERRAL CASES

Referral cases (12) formed 11% of total cases and 50% of gestational trophoblastic neoplasia. Of the referral cases 2(16.6%) were high risk metastatic GTN cases following term pregnancies and 10 were low risk GTN cases (83.3%).

Of the low risk GTN cases referred, 7 cases (58.3%) were following complete mole and 2 cases (16.6%) were following partial mole. One case (8.3%) was following missed abortion (Chart-3).

ANTECEDENT PREGNANCY

The antecedent pregnancy was hydatidiform mole in 83.3% cases of low risk GTN except the ETT in which the live birth was remote (Chart-4).

The antecedent pregnancy was abortion in one case of low risk GTN (4.1%).

Chart-3:

REFERRAL CASES (12)

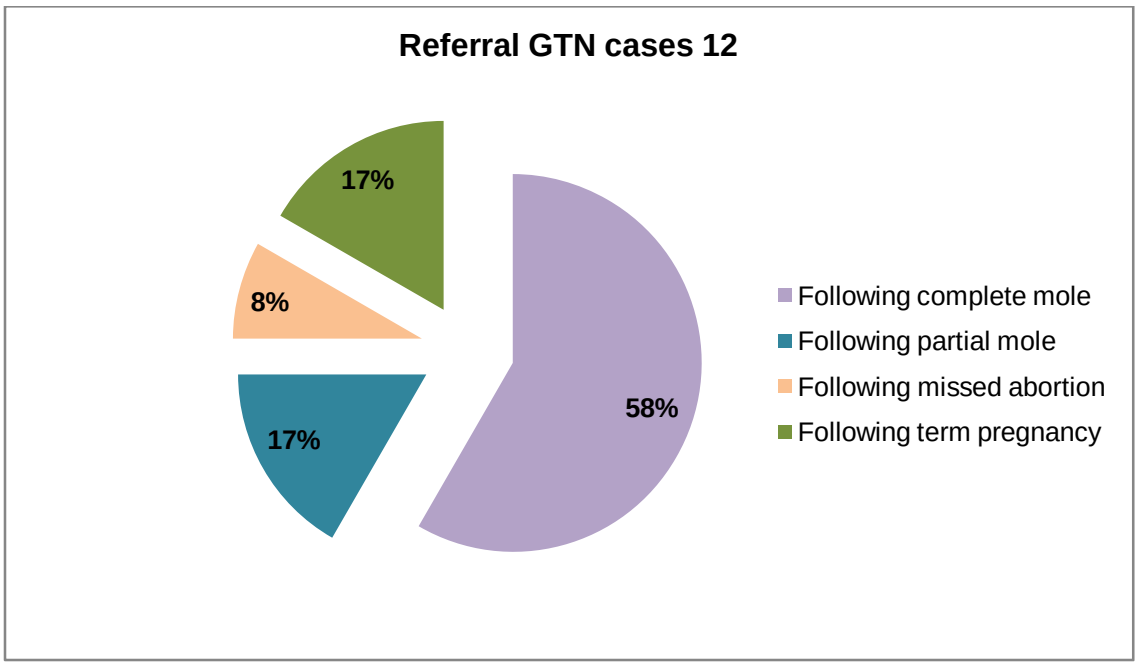
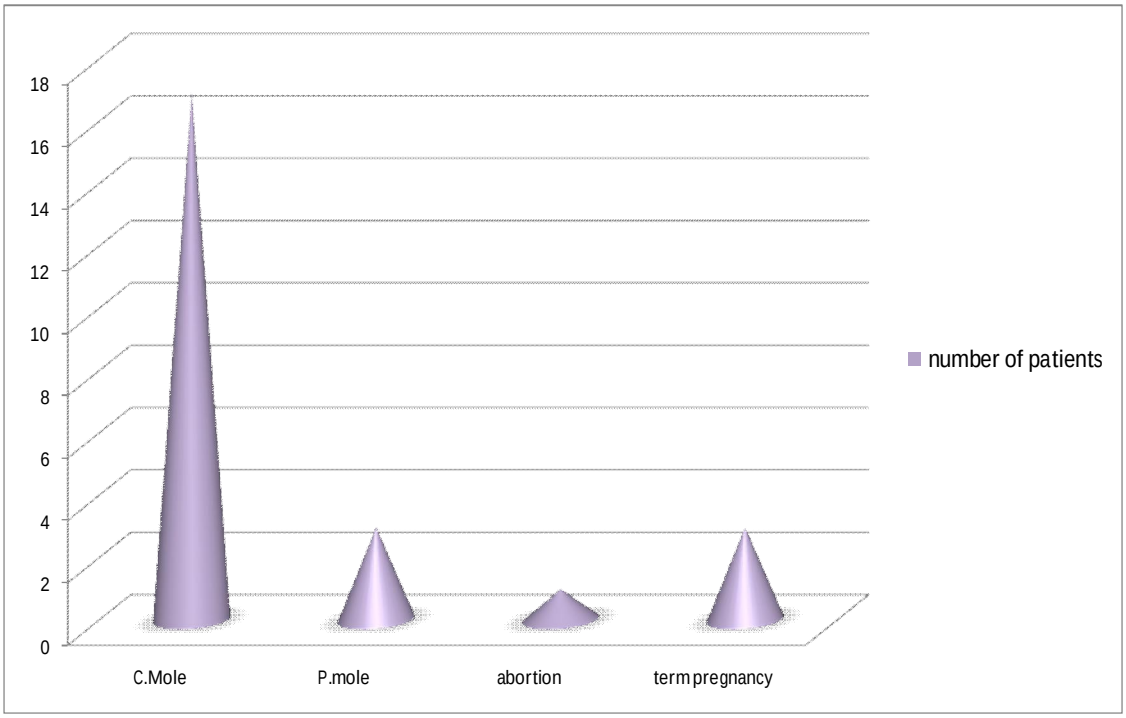


Chart-4:

ANTECEDENT PREGNANCY IN 24 TREATED GTN CASES



The antecedent event was full term pregnancy in both high risk metastatic GTN cases and low risk epithelioid trophoblastic tumor (12.5%).

AGE DISTRIBUTION OF WOMEN WITH GTD

Most cases (81%) presented between 20- 29 years which is the peak fertility group (mean24.5 years). 9% of the cases were below 20 years and another 9% of cases were above 30 years. Only one case presented beyond 40 years of age (chart-5).

Age Group	**No. of Cases**	**Percentage**
Below 20 years	11	9.5%
20 to 29 years	92	81%
30 to 39 years	10	8.6%
More than 40	1	0.9%

PARITY OF WOMEN WITH GTD

In 31.5% of cases, molar pregnancy was their first conception. It is after one live birth in 31.5% of cases and two live births in 21% of cases.7% (8 cases) of molar pregnancies were after an abortion and there were four (3.5%) repeat molar pregnancies.

Chart 5:

AGE DISTRIBUTION OF WOMEN WITH GTD

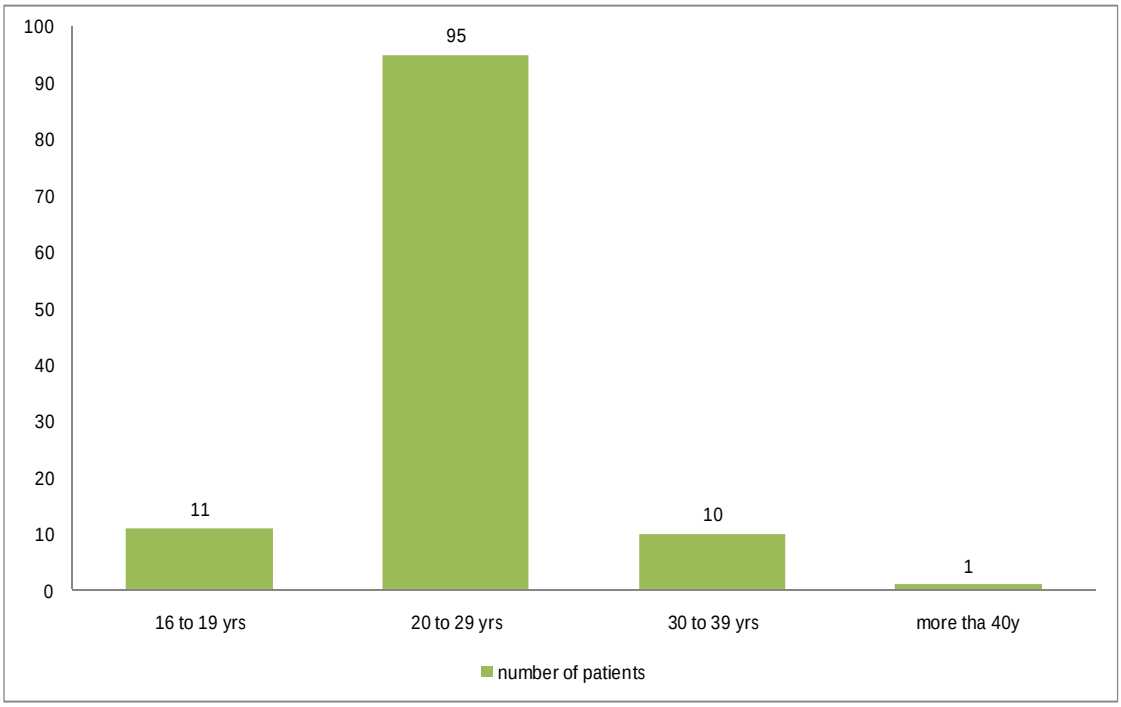
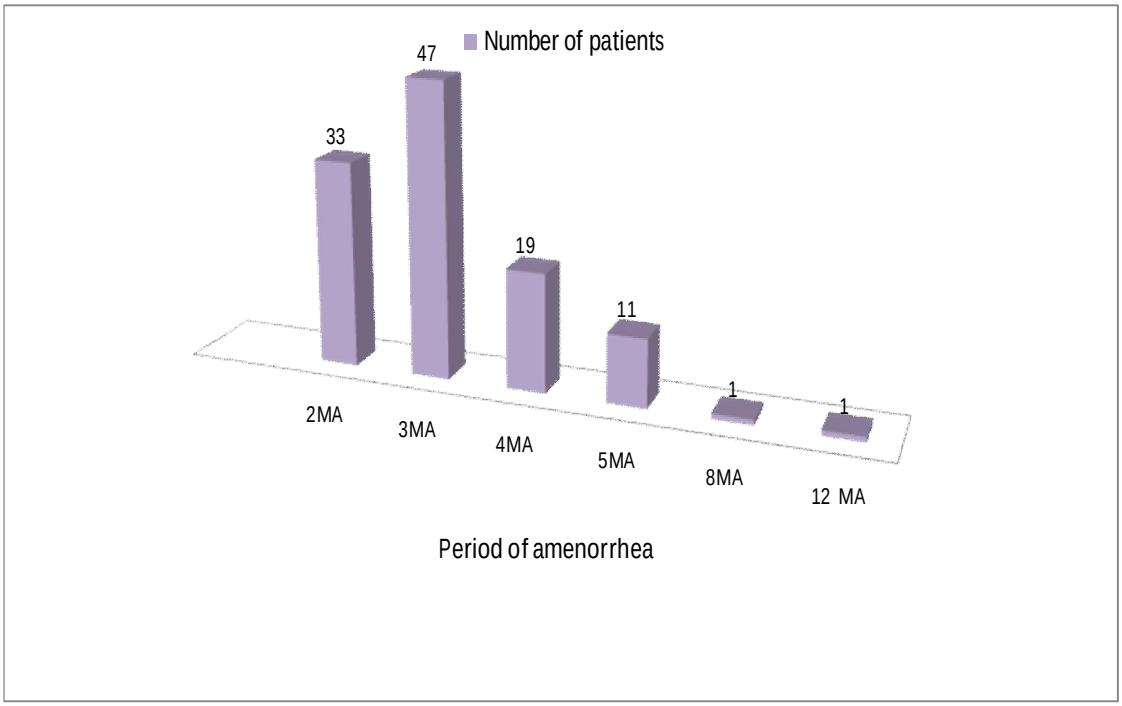


Chart :6 :

PERIOD OF AMENORRHOEA AT PRESENTATION



PARITY	NO. OF CASES	PERCENTAGE
Primi	36	31.5%
Gravida 2	36	31.5%
Gravida 3	24	21%
Gravida 4	5	4.3%
Gravida 6	1	0.8%
Abortion	8	7%
Repeat mole	4	3.5%

Three out of the four repeat mole (75%) had developed post molar GTN.

PRESENTING SYMPTOMS

In 51% of the cases the molar pregnancy was diagnosed in routine early first trimester ultrasound in asymptomatic women with history of amenorrhea. It presented as bleeding or spotting per vagina in another 48% of cases. Epithelioid trophoblastic tumor presented as foul smelling vaginal discharge.

Asymptomatic on routine first trimester ultrasound	52(51%)
Bleeding or spotting p/v	49(48%)
Foul smelling vaginal discharge	1(0.9%)

GESTATIONAL AGE AT PRESENTATION

Most of the cases (64%) had a history of 2 - 3 months amenorrhea. Twins (fetus with coexisting mole) presented at 8 months amenorrhea.

Epithelioid trophoblastic tumor had a history of one year of amenorrhea. 23.2% of patients presented with a history of 4 - 5 months amenorrhea (Chart 6).

Period of amenorrhea	No. of patients	%
2months	33	26.4%
3months	47	37.6%
4months	19	14.4%
5months	11	8.8%
8months	1	0.8%
12months	1	0.8%

UTERINE SIZE AT EVACUATION (Chart 7)

In 56% of the cases the uterine size at evacuation was below 14 weeks. In 37.3% of the cases the uterine size was between 14 to 20 weeks. The uterine size was between 21 and 28 weeks in 7 cases (6.8%).

27% of molar pregnancies with uterine sizes more than 20 weeks developed post molar GTN while 5.3% of the cases with uterine size less than 20 weeks had post molar GTN.

Uterine size	No. of patients	Percentage
<14 weeks	57	55.9%
14to 20 weeks	38	37.3%
21 to 28 weeks	7	6.8%

UTERINE SIZE IN RELATION TO PERIOD OF AMENORRHEA

In 55.2% of cases, uterus was bigger than the period of amenorrhea and 7.8% of cases uterus was smaller than the period of amenorrhea. 36.8% uterus was corresponding to the period of amenorrhea.

Uterine size	Number of cases	Percentage
Corresponding to GA	42	36.8%
Big(More than GA)	63	55.2%
Small (less than GA)	9	7.8%

Chart7:

UTERINE SIZE AT EVACUATION

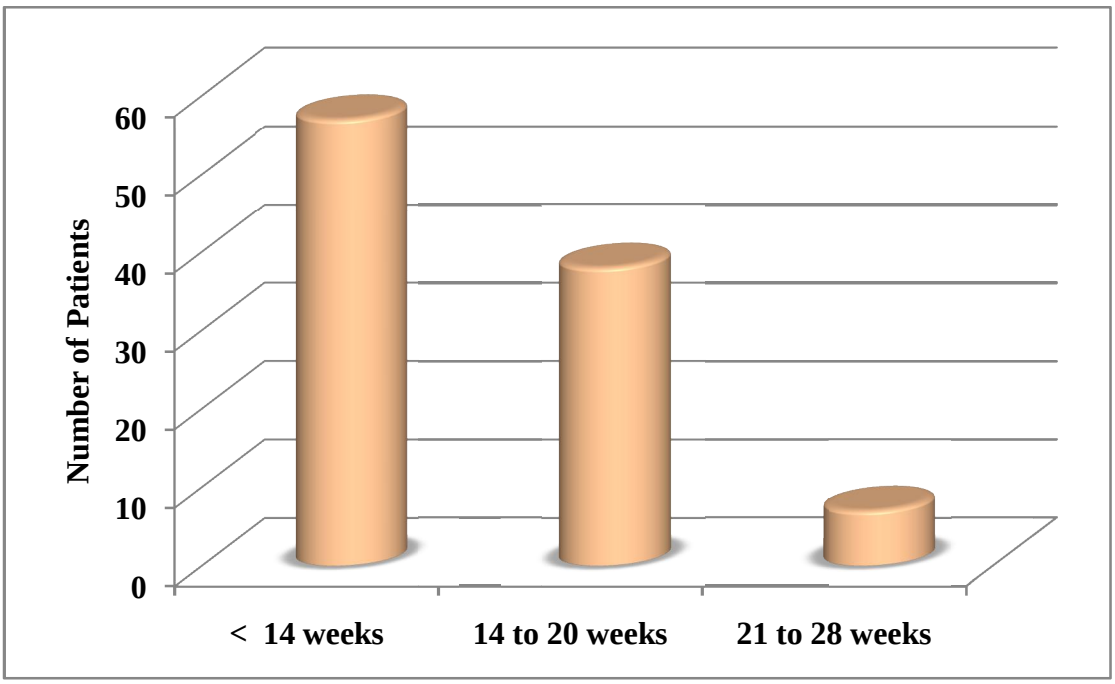
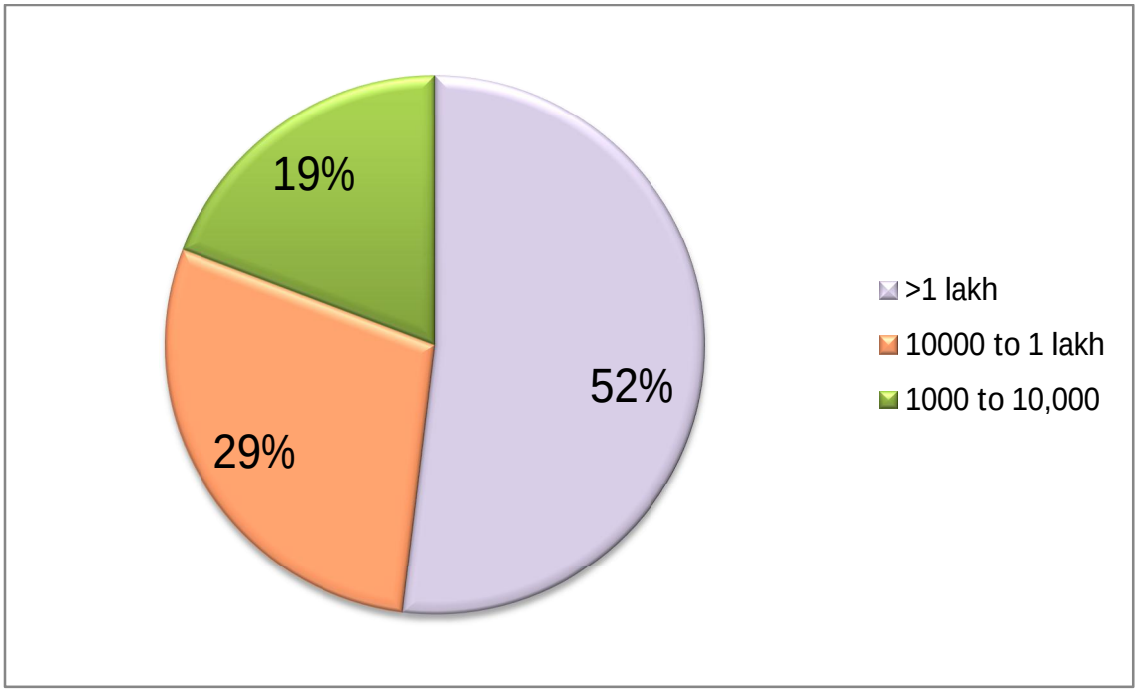


Chart 8:

PRE EVACUATION β hCG VALUES



MEDICAL COMPLICATIONS

Anemia requiring blood transfusion was present in 20 (17.5%) cases. Fetus with coexistent mole had preeclampsia since 5 months of gestation. Vomiting requiring anti emetic therapy was present in 21(18%) cases. Biochemically proven symptomatic thyrotoxicosis was present in 2 (1.6%) cases. Three (2.4%) patients suffered cough / wheeze during and after evacuation.

Complications	**Number of cases**	**Percentage**
Anemia	20	17.5%
Vomiting	21	18%
Theca leutin cyst<6cms	9	7.2%
Thyrotoxicosis	2	1.6%
Cough/wheeze	3	2.4%
Preeclampsia	1	0.8%

Ultrasound detected theca leutin cyst (< 6 centimeters) was present in 9(7.2%) cases. 44.4% of patients with bilateral theca leutin cysts developed post molar GTN after evacuation.

PRE EVACUATION β hCG VALUES

β hCG values	No. of patients	%
> 1 lakh	54	52%
10.000 to1lakh	30	28.8%
1000 to 10,000	20	19.2%

Pre evacuation β hCG was more than one lakh in 52% of cases and between 10,000 and one lakh in 28.8% of cases and below 10,000 in 19.2% of cases. The mean initial β hCG was 171,915mIU/ml.

11.2% of the molar pregnancies with β hCG more than one lakh developed post molar GTN (Chart 8).

TIME TAKEN FOR β HCG TO NORMALIZE IN NORMAL MOLAR PREGNANCIES

Weeks to normal	No. of cases	Percentage
8 to 12 weeks	50	67.6%
13to 16 weeks	22	29.7%
17 to 20 weeks	2	2.7%

Chart 9:

TIME TAKEN FOR β hCG TO NORMALISE IN UNEVENTFUL H.MOLE

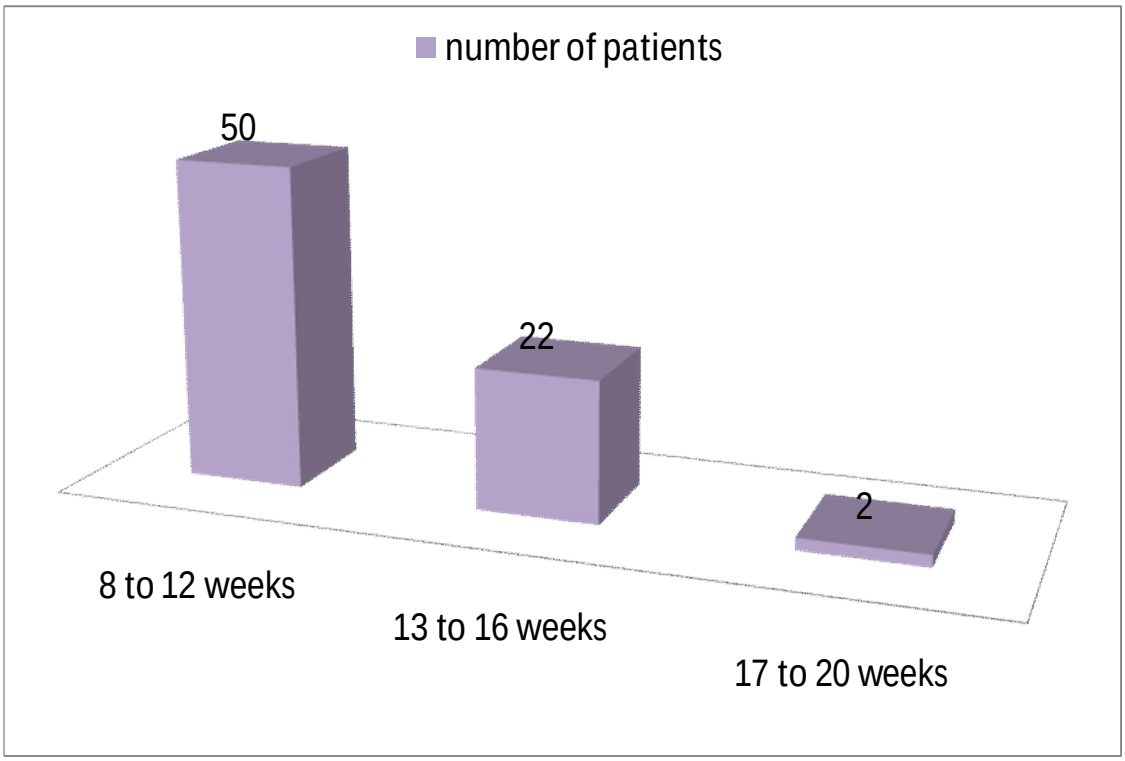
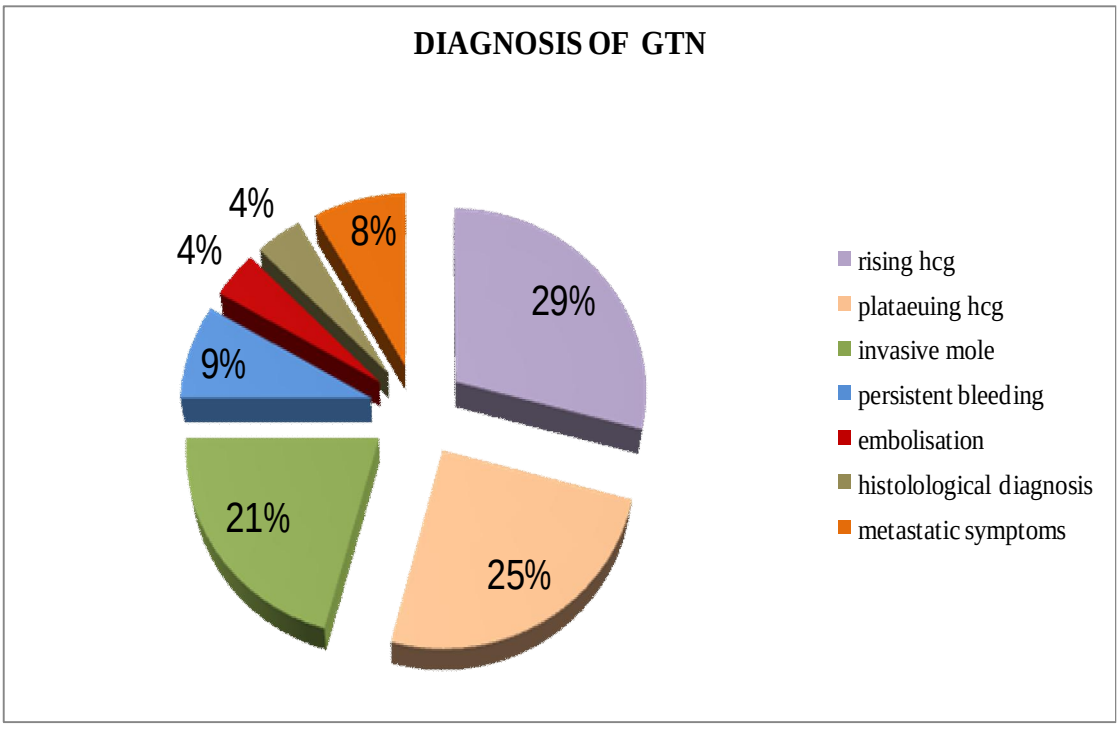


Chart 10:



In 67.6% of the uneventful molar pregnancies, it took 8 to 12 weeks (average of 10 weeks) for the return of β hCG to normal level (Chart-9).

29.7% cases took an average of 14.5 weeks (13 to 16 weeks) to normalize. In two patients (2.7%) the average time taken for the β hCG to normalize was 18.5 weeks (17 to 20 weeks).

DIAGNOSIS OF GTN

Both the high risk GTN cases after term pregnancy, presented 5-6 months after live birth with metastatic symptoms like breathlessness, cough and neurological symptoms like headache, giddiness and projectile vomiting. Both were treated outside for persistent vaginal bleeding after delivery by check curettage (Chart 10).

Diagnosis of GTN	**No. of cases**	**% of low risk GTD**
Rising value of β hCG	7	31.8%
Plateauing of β hCG	6	27.3%
Embolic manifestation	1	4.5%
Persistent bleeding with uterine disease	2	9%
Histological diagnosis	1	4.5%
Invasive mole(doppler)	5	22.7%
Metastatic symptoms (High risk GTN)	2	

In 31.8% of low risk GTN, the diagnosis was made by rising β hCG values. In 27.3% of patients with low risk GTD, there was plateauing of β hCG values during follow up.

There were 5 cases (22.7%) of invasive mole diagnosed with doppler ultrasound. All the five cases were diagnosed during follow up at IOG.

Patient with epithelioid trophoblastic tumor underwent hysterectomy for profound sepsis and postoperatively diagnosed histopathologically as ETT. Immunohistochemistry was done to confirm the diagnosis.

One case presented with breathlessness and cough due to trophoblastic embolisation during suction evacuation. It was managed with 100% oxygen ventilation and with bronchodilators.

β hCG REGRESSION CURVE

A log value regression curve was developed from the means and 95% confidence limits of serial monthly serum β hCG titers of 72 patients with uneventful hydatidiform mole and 12 patients who were previously confirmed as GTN.

All 12 GTN patients (100%) had abnormal values beyond normal range from the beginning (Chart 11).

MEAN AND STANDARD DEVIATION OF SERIAL MONTHLY

β hCG OF 72 PATIENTS WITH UNEVENTFUL MOLAR PREGNANCIES

	Initial	**4th week**	**8th week**	**12th week**	**16th week**	**20th week**
N	72	72	71	60	25	3
Mean	27019.09	2653.113	116.80	4.46	.06	.00
Median	23294.50	500.000	3.90	.00	.00	.00
Std. Deviation	19913.154	5631.4232	414.603	14.218	.187	.000
Minimum	1029	1.3	0	0	0	0
Maximum	91139	36131.0	2658	94	1	0

MEAN AND STANDARD DEVIATION OF SERIAL MONTHLY

β hCG IN 12 PATIENTS WITH PTD

	N	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Initial	12	410.00	471622.00	131448.2	199702.70468
4 weeks	12	56.00	97507.00	17211.43	29131.76072
8 weeks	11	18.00	148339.00	19527.69	46170.273272
10 weeks	9	10.00	50469.00	6093.3289	16660.92304
12 weeks	6	8.00	14782.00	2754.1667	5906.44297
16 weeks	6	2.90	553.00	172.5533	247.62833

Chart 11:

β hCG REGRESSION CURVES IN NORMAL MOLAR PREGNANCIES Vs. GTN

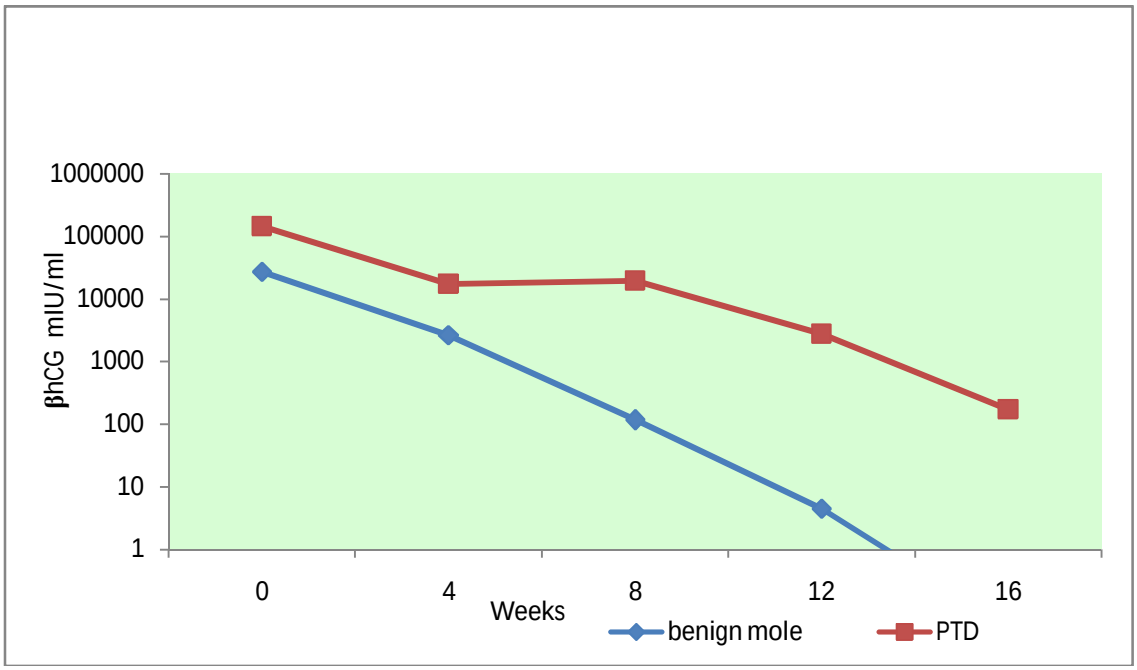
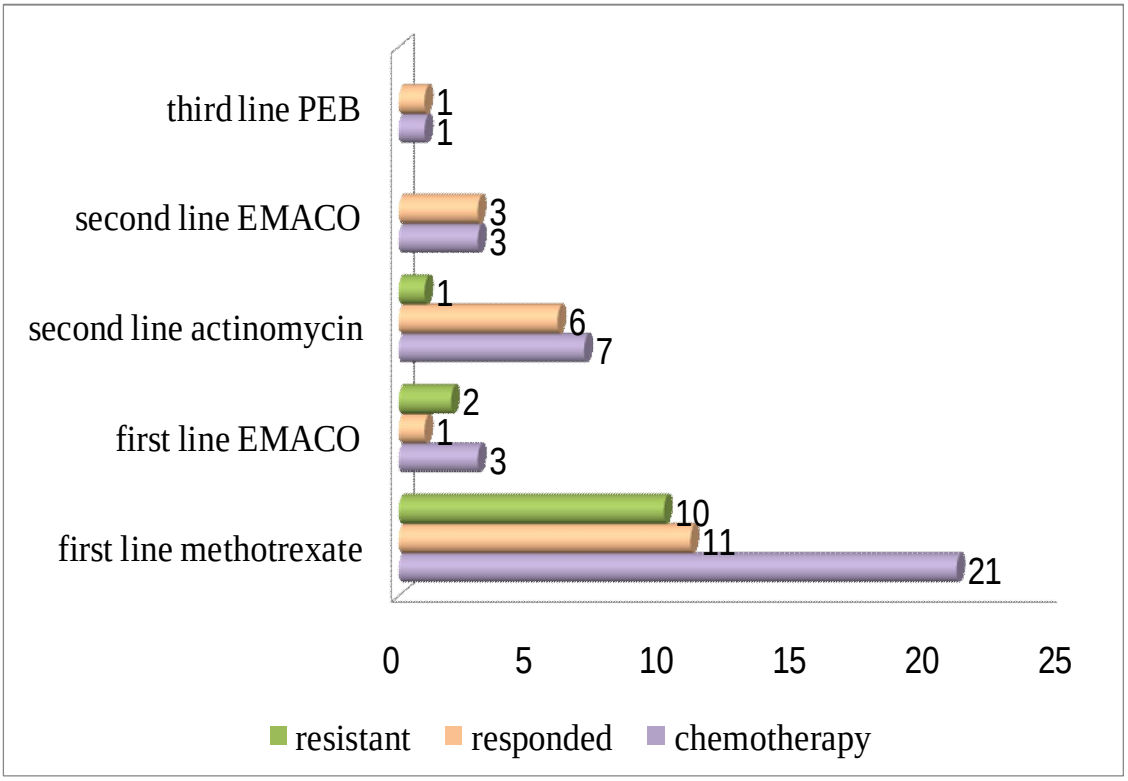


Chart 12:

CHEMOTHERAPY RESPONSE



WHO SCORES IN GTN

WHO score	No of patients	Percentage
0	5	22.7%
1	8	36.4%
2	5	22.7%
3	2	9.09%
5	1	4.5%
6	1	4.5%
10(high risk)	1	
17(high risk)	1	

In 60% of the cases the WHO risk score was 1and 2. In 9% of the cases the WHO score was 5 and 6. In another 9% of the cases the WHO score was 3. The WHO score was 0 in 22.7% of patients (5 cases).

METASTASIS

Both the high risk GTN cases after full term pregnancy had lung, brain and vaginal metastasis at presentation.

The high risk GTN case with progressive disease developed spinal cord metastasis and new brain metastasis while on treatment.

The lung and vaginal metastasis in both high risk GTN cases disappeared after treatment with EMA-CO.

Both the high risk cases received cranial irradiation (3000cGY) in 10 fractions for brain metastasis

Site of metastasis	**Number of cases**
Lung metastasis	2
Brain metastasis	2
Spine metastasis	1
Vaginal metastasis	2

High risk GTN (metastatic) case-1

- 20 year old , para 1, live 1, presented 5 months after child birth by full term vaginal delivery at arakkonam GH with complaints of persistent bleeding per vagina since delivery, headache, giddiness, projectile vomiting.
- Check curettage was done outside for retained placental bits 2 months after delivery and the histopathology report was inconclusive.
- CT Brain and Chest x- ray showed multiple brain and lung metastasis.
- Her initial β hCG was 1648 mIU/ml.
- Her WHO risk score was 10.

Figure - 16

MRI of Lumbosacral Spine showing hemorrhagic intradural metastasis

Figure - 17
Vaginal metastasis in GTN

- She was treated with 7 cycles of EMA-CO, 3 cycles of intrathecal methotrexate 12.5mg and high dose methotrexate (1g) twice.
- She was treated with 3000cGy of brain irradiation in 10 fractions.
- While on treatment, MRI Spine was taken because of severe back pain which showed intradural hemorrhagic metastasis at L1-L2.
- She received 10 fractions of lumbar spine irradiation and salvage chemotherapy (3 cycles) with cisplatin and paclitaxol.
- She developed paraparesis with bladder incontinence due to spinal metastasis.
- She expired 14 months after diagnosis due to progressive disease.

High risk GTN (metastatic) case-2

- 26 years old, para1live 1abortion1 presented at 6 months after child birth by full term LSCS at KGH presented with complaints of breathlessness and persistent bleeding per vagina since delivery.
- Check curettage was done in a private hospital 3 months after delivery for retained bits of placenta. The histopathology report showed endometrial glands in proliferative phase with no evidence of chorioic villi.
- Her initial β hCG was 2, 25,000 mIU/ml.
- She had sub uretheral nodules and vaginal metastasis.
- Chest X-ray and CT brain showed multiple hemorrhagic metastases.

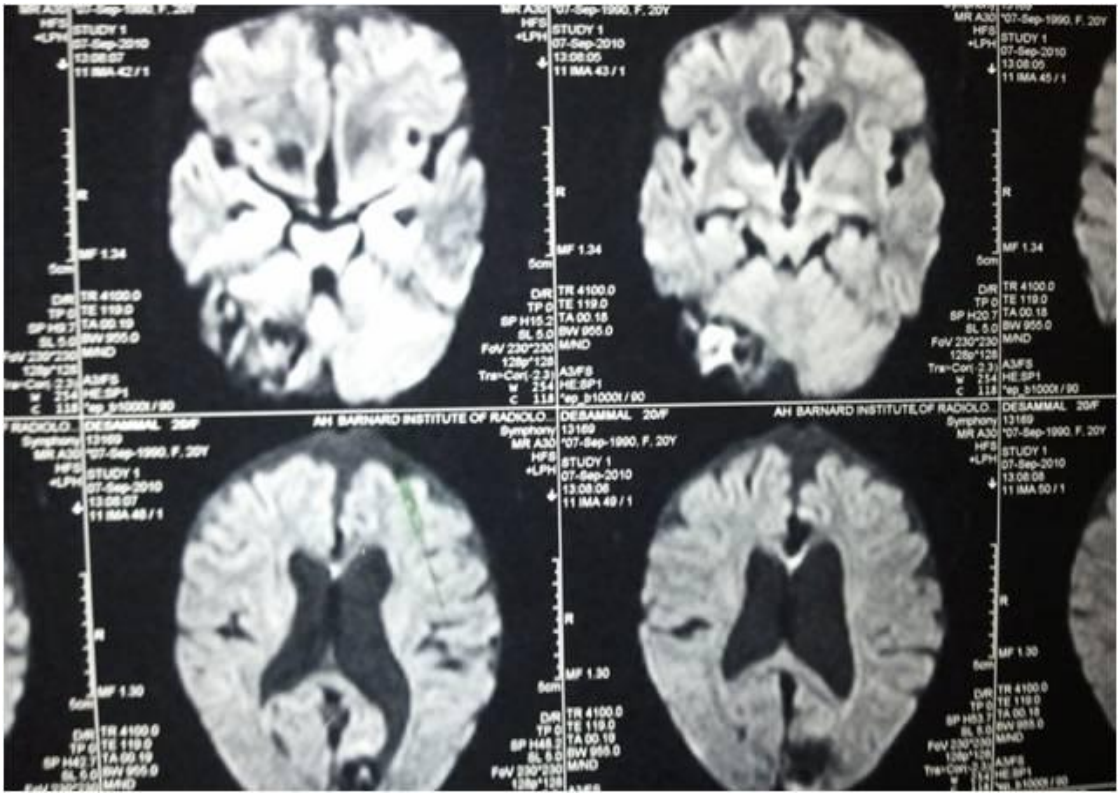
- The WHO Score was 17.
- She was treated with 4 cycles of EMA-CO, 3 cycles of PEB, 7 cycles of VIP, and salvage chemotherapy with cisplatin and cyclophosphamide.
- She received 10 fractions of cranial irradiation (3000 cGys).
- Her CT brain taken after treatment was normal.
- Now her serum β hCG values are undetectable. She is on follow up

Epithelioid trophoblastic tumor

- 28 year old, para 1,live1 ,abortion1, with last child birth 10 years back, presented with complaints of one year of amenorrhea and foul smelling discharge per vagina for 6 months.
- Her general condition was poor.
- The uterus was irregularly enlarged to 24 weeks.
- Her initial β hCG was 50,938.
- Ultrasound revealed a mass in uterus with multiple air pockets.
- Her Chest x-ray was normal.
- Total abdominal hysterectomy was done for profound sepsis.
- The gross appearance of the uterus specimen revealed a mass in uterus with extensive necrosis and turbid fluid.

Figure – 15

MRI Brain showing hemorrhagic metastasis in high risk GTN



- The histopathology report was suggestive of epithelioid trophoblastic tumor.
- Immunohistochemistry done showed cytokeratin 7+ ve ,

  Ki 67 -10-15%, P63- 70-80%.
- Her WHO risk score was 5.
- She was treated with 10 doses of weekly intramuscular methotrexate .
- Her general condition improved after treatment.
- Her β hCG values are undetectable for the past 9 months.

GESTATIONAL TROPHOBLASTIC NEOPLASIA (24 CASES)

TREATED AT IOG

GTN following	**IOG (12)**	**Referral (12)**	**Total**
Complete Mole	10	7	17(77.3%)
Partial Mole	1	2	3(13.6%)
Epithelioid tumor after live birth	1	-	1(4.5%)
Following abortion	-	1	1(4.5%)
High Risk GTN(metastatic)	-	2(following term pregnancy)	2

Figure - 6

Doppler of the vessels shows the invasion of the thin uterine wall

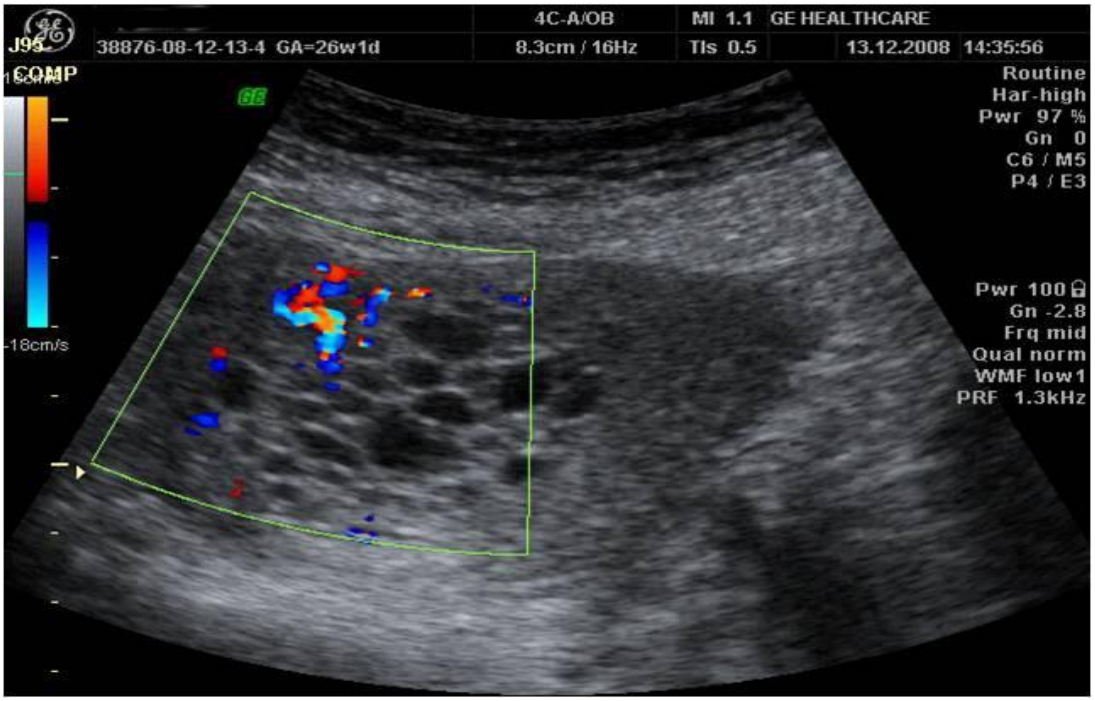


Figure – 7

Gross appearance of Invasive mole, hemorrhagic mass in the myometrial wall

Invasive mole at IOG	5
1, Following Complete mole	4
2, Following Partial mole	1

Invasive mole constitutes 4.9% of the total molar pregnancies at IOG and 41.7% of low risk GTN cases at IOG.

They constitute 22.7% of total treated GTN cases and no cases of invasive mole was referred from outside.

CHEMOTHERAPY FOR 24 GTN CASES

Single agent weekly methotrexate	21
Direct EMA-CO for low risk GTN	1
EMA-CO for high risk GTN	2
Resistant to weekly methotrexate	10 low risk GTN
Second line actinomycin D every 2 weeks	7
Second line EMA-CO	3
Third line PEB for actinomycin D resistance	1

Of the 22 low risk GTN cases, single agent weekly intramuscular methotrexate 50mg was given for 21 patients and direct multi agent chemotherapy EMA-CO was given for one low risk GTN patient who had a

distinct vascularisation of uterus in doppler . The mean numbers of chemotherapy cycles given were 8.5 (Chart 12).

Of the 21 methotrexate treated patients, 11 patients (52.3%) achieved complete remission with methotrexate.

Of the 10 methotrexate resistant low risk GTN cases, 7 patients received second line chemotherapy with actinomycin D every two weeks. Out of the 7 patients treated, 6 (85.7%) patients achieved complete remission with actinomycinD.

Second line EMA-CO was given to 3 patients with methotrexate resistance and all three patients responded to it.

Third line PEB regimen was given for a case with actinomycin resistance and the patient got cured of disease.

All patients who had undergone repeat curettage for uterine disease and three of the invasive mole did not respond to first line single agent methotrexate.

Two repeat molar pregnancy cases who developed GTN did not respond to single agent methotrexate.

Drug toxicities like oral ulcers and mucositis were present in 33% (8 patients) of treated low risk GTN patients and gastrointestinal disturbances

like vomiting and diarrhea were reported in 16.6% (4 patients) of low risk GTN patients.

Three (12.5%) low risk GTN patients had alopecia. Both the high risk GTN patients had alopecia, gastrointestinal disturbances, oral ulcers and myelosuppression, and both were treated with filgrastim.

All drug toxicities were grade 1 or 2.

Both the high risk GTN cases did not achieve complete remission with EMA-CO regimen and were given platinum based regimens.

ASSOCIATED CONDITIONS

Associated conditions	Number of patients
• ANA +ve nephropathy	1
• AION of right eye	1
• Rheumatic heart disease	4
• HbsAg +ve	1
• HIV + ve	1
• Bicornuate uterus	2

We had 3 cases of rheumatic heart disease complicating molar pregnancies.

There were two cases of bicornuate uterus with molar pregnancy. Ultrasound guided suction evacuation was done in both the cases.

Three cases of atypical placental site nodules were registered for follow up. All the 3 cases spontaneously expelled the dead fetus at 6-7 months of gestation and placenta along with a solid mass and were histopathologically diagnosed as benign chorioangioma.

OUT COME

Outcome	**Number of cases**
Completed follow up	4
Pregnancy during follow up	4
On follow up	88
Defaulters	16(15.6%)
On Chemotherapy	1
Expired high risk GTN	1
Quiescent GTD	1

At a mean follow up of 18 months, 4 patients had completed follow up. Four patients were non compliant with the contraceptive measures and became pregnant during follow up.

16 patients (15.6%) were lost to follow up including one low risk GTN.

One low risk GTN patient is on chemotherapy.

90 patients are on regular follow up which includes 21 cases of low risk GTN cases (95.5%low risk GTDs), one case of high risk GTN and 66 benign molar pregnancies (73.3% of normal molar pregnancies).

One patient had persistent low levels of β hCG (Quiescent disease).She was thoroughly investigated for occult disease and is being closely followed up.

One patient died of progressive high risk metastatic disease due to late presentation in advanced disease, 14 months after the diagnosis.

One patient with low risk GTN on chemotherapy defaulted as her husband got transferred to Bangalore and is advised treatment there.

One patient (3^{rd} gravida with two live children) underwent sterilization 6 weeks after molar evacuation.

DISCUSSION

The incidence of molar pregnancies at IOG is 5 per 1000 pregnancies.

The reported incidence of GTD varies worldwide from a low of 0.23/1000 in Paraguay to a high of 12.99/1000 in Indonesia (Alteiri A et al) [56].

The incidence of hydatidiform mole is 5.3 per 1000 deliveries in a 15 year study done at the Calicut Medical College (Shekheran P K et al) [15].

In a study from Pakistan by Marukh Fatima et al in 2011[58], the incidence of molar pregnancies is 5.1 per 1000 pregnancies.

In a survey conducted in China including 143 hospitals, the incidence of GTD was 3.87 /1000 pregnancies. (Shi YF et al et al).[57].

The hospital based incidence reported from certain teaching hospitals in India shows an incidence of 1 in 150 to 1 in 300 deliveries (Shekheran PK et al) [15].

A study, by Smith HO et al, there is a relationship between ethnicity and risk of molar pregnancy and incidence is highest in American Indians, Eskimos and Asian population.[59]

This increased incidence in Asians is due to unfavorable socio economic and nutritional factors.

Of the 102 IOG cases, 80 cases (78.4%) were complete mole, 21cases (20.5%) were partial mole and one (0.9%) was a case of ETT. 4.9% of the total GTD cases at IOG were invasive mole.

In our study, most cases (81%) presented between 20- 29 years which is the peak fertility group (mean24.5 years).

In the Chinese Survey of GTD among 3.6 million pregnancies, the GTD cases mainly occurred among 20-34 year old women.[57]

In a study by Soares PD et al, GTD predominated in the peak fertility age group (20-34 years) and among patients of unfavorable socioeconomic status.[60]

The risk associated with maternal age is bimodal with increased risk for both less than 20 years and more than 35 years. The relative risks are in the range of 1.1 to 11 (Altman AD et al 2008). [61]

In our institution, most of the cases (64%) had a history of 2 and 3 months amenorrhea.

In 56% of the cases the uterine size at evacuation was below 14 weeks. In 37.3% of the cases the uterine size was between 14 to 20 weeks and the uterine size was between 21 and 28 weeks in 7 cases (6.8%).

In our institution, 27% of the patients with uterine size 20 weeks or more developed post molar GTN. In uterine sizes more than 24 weeks at evacuation, one third of the patients developed post molar GTN.

25% of patients with large for dates uterus developed GTN compared to 11% of patients with small for dated uterus (Berkowitz RS et al) [9].

Soto Wright et al demonstrated a reduction in the mean gestation at presentation from 16 weeks in 1970s to 12 weeks in 1990s.[62]

In our study, 51% cases of molar pregnancy were diagnosed in routine early first trimester ultrasound in asymptomatic women with history of amenorrhea. Patients with GTD presented as bleeding or spotting per vagina in another 48% of cases.

Routine pre-evacuation ultrasound examination identifies less than 50% of hydatidiform mole, the majority sonographically appearing as missed miscarriage or blighted ovum. Detection rates are, however, higher for complete compared to partial mole, and improve after 14 weeks' gestation.

Histopathological examination of products of conception remains the current gold standard for the identification of gestational trophoblastic diseases (Fowler DJ et al 2006).[30]

The use of serum β hCG as a screening tool to identify those women with anembroyonic pregnancies would enable us to counsel women more confidently towards non-surgical methods of management if the β hCG is low. It would also provide us with a useful follow-up tool for those cases in which histopathological assessment is not possible (John J et al).[29]

At our institution, 17.5% of patients had anemia and 18%of cases had vomiting requiring antiemetic treatment. Only 2 cases (1.6%) had features of hyperthyroidism and one patient (0.8%) had preeclampsia. Respiratory

symptoms were present in 2.4% cases and sonographicaly detected theca leutin cysts (less than 6 centimeters) in 7.2% of cases.

Nowadays, fewer patients with complete hydatidiform mole present with the traditional symptoms of complete hydatidiform mole (excessive uterine size, anemia, preeclampsia, hyperthyroidism, or hyperemesis). However, there has been no statistically significant change in the development of persistent gestational trophoblastic tumor in current patients (Hou J L et al).[31]

In our study, a log value regression curve was developed from the means of serial monthly serum β hCG titers of 72 cases of normal uneventful molar pregnancies and 12 low risk GTN cases.

A normal regression curve may help the physician to decide on a single random value and to change the intervals of follow up visits in selected patients.

It may also facilitate the earlier recognition of GTN, than the plateau or rise of level of β hCG (Behtash N et al).[48]

In our study, in 97.3% of normal molar pregnancies, the serum β hCG reached normal values in 8 to 16 weeks.

Several authors have described serum β hCG concentrations to be normalized in 50% of patients between 6 and 14 weeks after evacuation. (Behtash N et al).[48]

Approximately 50% of patients with complete mole have pre evacuation β hCG levels 100,000 mIU/mL (Lurain JR et al).[7]

At our institution, pre evacuation β hCG was more than one lakh in 52% of cases and between 10,000 and one lakh in 28.8% of cases.

We had a case of twin gestation with complete molar pregnancy. She was diagnosed during routine ultrasound at 6 months amenorrhea. Ultrasound showed diamniotic dichorionic twin pregnancy, one sac showing structurally normal fetus (24 weeks) with normal placenta and another sac showing a complete mole (20*10*9cms).Her initial β hCG was 24,888mIU/ml.

She developed pre-eclampsia at 26 weeks and was treated with antihypertensives. At 30 weeks of gestation, patient spontaneously delivered a live boy baby (720grams) with good apgar. Baby died 5 days after birth due to extreme prematurity and hyaline membrane disease. About 2 kg of cystic vesicular tissue was evacuated from the uterus with normal placenta after delivery of the baby. Her β hCG values became undetectable by 8 weeks after delivery.

Complete mole and co-twin pregnancies have a high risk of spontaneous abortion, but about 40% result in live births, without significantly increasing the risk of GTN (Sebire NJ et al).[65]

Evidence comparing early versus delayed evacuation of molar pregnancy suggest that delayed termination has no increased risk of malignant disease (Seckl MJ et al) [66].

This suggests that molar pregnancies are probably preprogrammed to behave malignantly at an early stage of development before uterine evacuation.

So, oxytocin infusion during evacuation helps to minimize bleeding without increased risk of persistent disease (Shekheran PK et al) [3]. An oxytocin infusion may be started before induction of anesthesia to facilitate contraction and thus decrease blood loss.

Concern has been expressed that oxytocin may promote metastasis of trophoblastic tissue. However, it has been reported that uterine stimulation during evacuation did not increase the risk of persistent tumor (Shekheran PK et al) [13].

In our institution, we ripen the cervix with 200mg of misprostol four hours before molar evacuation and start oxytocin infusion at the beginning of evacuation.

We had four cases of repeat molar pregnancies constituting 3.5%of the total molar pregnancies. In one case, it was the fourth repeat molar pregnancy. It was the third molar pregnancy in two cases and the second molar pregnancy

in one case .Only the case with two molar pregnancies had a live birth before the mole

3 out of the 4 (75%) repeat molar pregnancies developed post molar GTN.

Women having a pregnancy affected by a histologically confirmed complete or partial hydatidiform mole may be counseled that the risk of repeat mole in a subsequent pregnancy is about 1 in 80 and the risk after two previous molar pregnancies is 1:6.5.

If this repeat mole is to occur, the majority of cases will be of the same type of mole as the preceding pregnancy.

However, >98% of women who become pregnant following a molar conception will not have a further hydatidiform mole and these pregnancies are at no increased risk of other obstetric complications (Sebire NJ et al)[65].

15.6% of the patients with molar pregnancies were lost to follow up in our study.

In a study from Al Quetta, Pakistan, 23% of the GTD patients were lost to follow up.

We counsel the patients and their family regarding the importance of follow up after evacuation of molar pregnancies and the need for

contraception throughout the follow up period and regarding their psychosocial issues.

Patients are lost to follow up mainly due to illiteracy, change of residence due to job transfers and social problems regarding the use of contraception.

The incidence of post molar GTN at our institution is 10.8% of molar pregnancies.

In a 15 year study from Calicut Medical College by Sekheran et al, the incidence of post molar GTN was 20.5%.[15]

A total of 22 low risk GTN cases and 2 high risk metastatic GTN cases were treated at IOG. Both the high risk GTN cases were referral cases after term pregnancy and presented with metastatic symptoms.

The incidence of persistent GTN after a live birth is estimated at 1 in 50,000 live births (Smith HO et al 2003).[64]

In our study, the antecedent pregnancy was hydatidiform mole in 20 cases (83.3%) of low risk GTN and abortion in one low risk GTN (4.2%).

The antecedent pregnancy was full term pregnancy in 12.5% of cases. In a study from All India Institute of Medical Sciences, New Delhi, the antecedent pregnancy was hydatidiform mole in 50% of GTN cases and

abortion in 34.3% of cases, and ectopic pregnancy in 4% of cases and term pregnancy in 11.8% of cases.

In our study, low risk GTN is diagnosed in 60% of cases as rising or plateauing β hCG values. In 22.7% of cases, invasive mole was diagnosed using doppler ultrasonography. Two cases had persistent vaginal bleeding after evacuation. One case had respiratory difficulty during evacuation.

Pulmonary complications at evacuation are caused by trophoblastic embolization or high output cardiac failure by anemia, hyperthyroidism, pre-eclamsia or iatrogenic fluid overload. They are treated aggressively by central hemodynamic monitoring and ventilator support as required (Soper TJ et al) [4].

In our study, Only ETT had histopathological diagnosis. Immuno histochemistry showed cytokeratin and p 63positivity.

The term 'epithelioid trophoblastic tumor' was originally introduced by Mazur and Kurman in 1994. In 1998, Shih and Kurman outlined the clinicopathologic characteristics of epithelioid trophoblastic tumor in 14 patients, and therefore established epithelioid trophoblastic tumor as a distinct entity within the category of gestational trophoblastic tumors. Since then, approximately 90 cases have been reported in the literature.

Histologic features include a nodular growth pattern of monomorphic, epithelioid cells within a hyaline matrix. Immunohistochemical staining

revealed strong diffuse reactivity for cytokeratins (CK7, CK18) , HLA-G and epidermal growth factor receptor, and focal reactivity, mainly in syncytiotrophoblastic cells, for β hCG , hPL and inhibin-α. Currently, we manage ETT in the same way as PSTT(Olewole F et al)[71].

The patient with quiescent GTD was a case of invasive mole diagnosed by doppler ultrasonography, treated with 13 cycles of weekly intramuscular methotrexate .Her β hCG values were undetectable for 3 months after which it is persistently low (<100 mIU/ml) for the past eight months. Her urine pregnancy test is positive. Her ultrasound and doppler of the abdomen and pelvis, chest x-ray, CT brain are normal. She is under close follow up.

Clinicians frequently assume that an elevated β hCG implies that a patient is pregnant or has GTD or recurrent GTN, even when apart from the pregnancy test, no clinical evidence was found to support such a diagnosis. In most of these cases of persistent low β hCG etiologies, all therapies were found unnecessary and ineffective.

It is essential to demonstrate a malignancy clinically and with readily available biochemical tests (β hCG >3000 IU/L) before initiating therapy. This applies whether the patient is identified by an incidental pregnancy test or is actively being monitored for gestational trophoblastic disease (Cole LA et al) [33].

In our study, the response rate to weekly intramuscular methotrexate in low risk GTN was 52.3%.The response rate to second line actinomycin D every 2 weeks was 85.7%.The response rate to second line EMA-CO was 100%.

In our study, one case with actinomycin D resistance was treated with PEB regimen.

In our institute, chemotherapy is continued until β hCG values have achieved normal levels, and an additional course is administered after the first normal β hCG value has been recorded (Soper TJ et al) [4].

The weekly intramuscular methotrexate regimen was as effective as the 8-day methotrexate-folinic acid regimen every 2 weeks for low-risk GTN. The weekly methotrexate regimen was less toxic, better tolerated, and more convenient for patients compared to the 8-day methotrexate-folinic acid regimen (Kang WD et al).[67]

In our study, the cure rate of low risk GTN patients is 100%. Apart from minor side effects, there were no drug toxicities in low risk GTN patients.

In a randomized phase 3 trial by the GOG , the response rate was 58% and 73% in the weekly methotrexate and actinomycin D arms respectively (Raymond JO et al 2011).[68]

In a retrospective study to examine the efficacy of single agent weekly intramuscular methotrexate , data support that methotrexate is the appropriate

first line therapy for low risk GTN irrespective of patient characteristics like age, race, metastasis, prior mole and β hCG values . The primary remission rate with weekly methotrexate was 54.2%.Failure of methotrexate has no impact on the eventual remission and patient survival, in patients requiring 2nd line chemotherapy (Q K Lippmann et al 2011).[69]

In our study, both the high risk GTN cases with brain and lung metastasis did not achieve complete remission with EMA-CO. Both were given salvage chemotherapy with cisplatin and ifosfamide containing regimens. One patient died of progressive disease.

Both the patients received cranial irradiation (3000cGy) in 10 fractions. High dose methotrextate (1g/sq.m) and intrathecal methotrexate (12.5mg) was given to the patient with progressive disease.

Evidence suggests that clinical complete response to EMA-CO in high risk GTN cases was influenced by

1, β hCG level (<100,000 mIU/ mL, 82%, vs.>100,000 mIU/mL, 46%),

2, Metastatic site (lung and pelvis, 75%, vs. other, 33%) and

3, FIGO risk score (<7, 92% vs.>7, 50%).

The overall survival rate was 80-90% in high risk GTN cases with initial EMA-CO, often in conjunction with brain irradiation, salvage chemotherapy and surgical resection (Lurain JR et al). [70]

SUMMARY

Since survival is 100%, patients should be first given the least toxic therapy.

- Due to lack of proper follow up and appropriate treatment, patient often present late in the disease where the outcome is going to be poor, hence the need for early referral to a specialized center.
- Patients with malignant GTN should be managed with complex multimodality treatment.
- A new prognostic test at the time of initial molar diagnosis is needed to identify those who develop malignant disease
- The prognosis and outcome of GTD is exceptionally good if diagnosed and treated in time with regular follow up primarily at a specialized center.
- Centralization of treatment would provide the opportunity to build clinical expertise on GTD, which would further improve outcomes in the management of GTN.
- The emotional, psychological, and social impact of the diagnosis of GTN on the patient and family should be addressed by counseling. This approach will ensure optimal holistic care for women with GTN.

CONCLUSION

- The incidence of gestational trophoblastic diseases had decreased over the past decade worldwide due to fall in birth rates and improved socioeconomic status.

- In considering clinical presentation, most patients are asymptomatic and are diagnosed during routine first trimester ultrasound.

- The ultrasound detection rate of molar pregnancy in first trimester is 56% and is imaged as blighted ovum or missed miscarriage. Hence the need for histopathological examination of products of conception in all anembryonic pregnancies.

- Serum β hCG is done in early pregnancy failures if there is a high suspicion of molar pregnancy. Otherwise urine pregnancy test at 4 weeks after termination is done in cases of early pregnancy failures where products of conception are not send for histopathology.

- Low risk GTN cases are 100% curable. There is no case of high risk disease at our institution .The patients are counseled on the need for follow up and contraception.

- Weekly intramuscular methotrexate regimen is highly effective in curing low risk GTN cases. Methotrexate is less toxic, inexpensive, and convenient to use and there is no need for hospitalization and patient compliance is better with the weekly methotrexate regimen.

- The incidence of molar pregnancies is 5 per 1000 pregnancies at IOG, as our institution is a tertiary referral center.
- The incidence of post molar GTN at IOG is 10.8% of molar pregnancies.
- All post molar low risk GTN cases are effectively treated with single agent weekly methotrexate, the failure of which is easily salvaged by second line monotherapy with actinomycin D.
- All low risk GTN cases are 100% curable. Overall survival is 100%
- There is a need for centralization of care with a regional registry and a central pathology review.
- It is important to manage molar pregnancies properly in specialized centers to minimize acute complications and identify malignant sequelae promptly.
- Follow up plays a major role to decrease morbidity associated with molar pregnancies.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. RCOG, Green Top Guidelines No.38, published on february 2010, The Management of Gestational Trophoblastic Diseases

2. Narendra Pisal, John Tidy, Barry Hancock, Gestational Trophoblastic diseases - Is intensive follow up essential in all women BJOG VOL I 11, Issue 12 pages 06 Oct 2004; 1449-1451.

3. Prof. SekharanP K, Review Article,Gestational Trophoblastic Diseases – The JOG India Vol 58 No.4 July/Aug 2008 ;299-307

4. Soper, John T MD, Clinic al expert series on Gestational Trophoblastic Disease Green Journal Obstetrics & Gynecology: July 2006- Volume 108 Issue 1;176-187.

5. Michael J Seckl, Neil J Sebire, Ross S Berkowitz Gestational trophoblastic disease Seminar July28 2010;doi :10.1016/so140-6736(10) 60280-2

6. Nienke E van Trommel,Charlotte Lybol,Chris M Thomas,Fred C Sweep Leon F Massuger; Diagnosis and Treatment of Gestational Trophoblastic Disease *European Obstetrics & Gynaecology*, 2011;6(1):28–32

7. John R. Lurain, MD Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease and management of hydatidiform mole. December2010 AJOG vol 6, 73:;531-539

8. Philip Savage, Molar pregnancy The Obstetrician and gynaecologist 2008 Jan Vol 10 Issue1;3-8.

9. Ross S Berkowitz, Donald P Goldstein, Molar pregnancy and Gestational trophoblastic neoplasms, Chapter 28,Principles and practice of Gynaecologic oncology 5 th edition;875-895

10. Gerulath H ,MD Gestational trophoblastic diseases SOGC Clinical Practice Guidelines, No. 114, May 2002,J Obstet Gynaecol Can 2002;24(5):434-9

11. Diagnosis and treatment of gestational trophoblastic disease. (ACOG); 2004 June ACOG practice bulletin; no. 53

12. Snyman LC ,Gestational trophoblastic disease: An overview SA Journal of Gynaecological Oncology 2009;vol.1no.1;32-37

13. Shekeran P K , ICOG, FOGSI Recommendations for good clinical practice,The Management of Gestational trophoblastic diseases,

14. Taymaa May, Donald P. Goldstein, Ross. S. Berkowitz; Current Chemotherapeutic Management of patients with Gestational trophoblastic Neoplasia; Chemotherapy Research and Practice Vol 2011; Article ID 806526 ;doi:10.1155/2011/806526:1-12

15. Sekharan P K ,Sreedevi N S, Radhadevi,VP,Management of Postmolar Gestational Trophoblastic Disease with Methotrexate and folinic acid,15 years of experience ,Journal of reproductive medicine, Vol51,no.10,October 2006,835-840

16. Tham BWL, Everard JE, Tidy JA, Drew D, Hancock BW. Gestational trophoblastic disease in the Asian population of Northern England and North Wales. BJOG 2003;110:555–9.

17. Kim SJ,Lee C ,Kwon SY, Na YJ ,Studying changes in the incidence, diagnosis and management of GTD: the South Korean model, J Reprod Med (2004) 49: 643-54.

18. Lybol C, Thomas CM, Bulten J, et al., Increase in theincidence of gestational trophoblastic disease in The Netherlands, *Gynecol Oncol*, 2011 May 1;121(2); 334-8

19. Sebire NJ, Foskett M, Fisher RA, et al. Risk of partial and complete molar pregnancy in relation to maternal age. Br J Obstet Gynecol 2002;109:99-102.

20. Kumar N, Saxena YK, Rathi AK, Chitra R, Kumar P. Host and risk factors for gestational trophoblastic disease: a hospital-based analysis from India. Med Sci Monit. 2003 Oct;9(10):CR442-7.

21. Hariprasad R,Ganessan K, Gupta A, Kumar L, Kumar S, Gestational trophoblastic disease: Experience at a tertiary care center from a developing country. *Journal of Clinical Oncology*, 2007 ASCO Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 16041

22. Parazzini F, Mangili G, La Vecchia C, Negri E, Bocciolone L, Fasoli M. Risk factors for gestational trophoblastic disease: a separate analysis of complete and partial hydatidiform moles.Obstet Gynecol. 1991 Dec;78(6):1039-45.

23. Sebire NJ, Fisher RA, Foskett M, Rees H, Seckl MJ, Newlands ES. Risk of recurrent hydatidiform mole and subsequent pregnancy outcome following complete or partial hydatidiform molar pregnancy, BJOG. 2003 Jan;110(1):22-6.

24. Fisher RA, Hodges MD, Newlands ES. Familial recurrent hydatidiform mole: a review.J Reprod Med. 2004 Aug;49(8):595-601

25. Palmer JR. Advances in the epidemiology of gestational trophoblastic disease J Reprod Med. 1994 Mar;39(3):155-62.

26. Ross S. Berkowitz MD , Marilyn R. Bernstein MHP, Bernard L. Harlow PhD, AJOGVolume 173, Issue 3, Part 1, September 1995, Pages 788-794

27. Gemer O, Segal S, Kopmar A, Sassoon E. The current clinical presentation of complete molar pregnancy Arch Gynecol Obstet. 2000 Jul;264(1):33-4.

28. Walkington L, Webster J, Hancock BW, Everard J, Coleman RE. Hyperthyroidism and human chorionic gonadotrophin production in gestational trophoblastic disease. Br J Cancer. 2011 May 24;104(11):1665-9.

29. Johns J, Greenwold N, Buckley S, Jauniaux E. A prospective study of ultrasound screening for molar pregnancies in missed miscarriages. Ultrasound Obstet Gynecol. 2005 May;25(5):493-7.

30 Fowler DJ, Lindsay I, Seckl MJ, Sebire NJ Routine pre-evacuation ultrasound diagnosis of hydatidiform mole: experience of more than 1000 cases from a regional referral center Ultrasound Obstet Gynecol. 2006 Jan;27(1):56-60.

31. Hou JL, Wan XR, Xiang Y, Qi QW, Yang XY Changes of clinical features in hydatidiform mole: analysis of 113 cases. J Reprod Med. 2008 Aug;53(8):629-33.

32. Fine C, Bundy AL, Berkowitz RS, Boswell SB, Berezin AF, Doubilet PM ,Sonographic diagnosis of partial hydatidiform mole. Obstet Gynecol. 1989;73(3 Pt 1):414.

33. Cole LA, Human chorionic gonadotropin and associated molecules. Expert Rev Mol Diagn. 2009 Jan;9(1):51-73.

34. Cole LA, Khanlian SA, Hyperglycosylated hcg: a variant with separate biological functions to regular hcg , Mol Cell Endocrinol. 2007 Jan 2;260-262:228-36. Epub 2006 Nov 1.

35. Harvey RA, Pursglove HD, Schmid P, Savage PM, Mitchell HD, Seckl MJ. Human chorionic gonadotropin free beta-subunit measurement as a marker of placental site trophoblastic tumor ,J Reprod Med. 2008 Aug;53(8):643-8.

36. Tidy JA, Gillespie AM, Bright N, Radstone CR, Coleman RE, Hancock BW. Gestational trophoblastic disease: a study of mode of evacuation and subsequent need for treatment with chemotherapy. Gynecol Oncol. 2000 Sep;78:309-12.

37. Elias KM, Goldstein DP, Berkowitz RS Complete hydatidiform mole in women older than age 50.J Reprod Med. 2010 May-Jun;55(5-6):208-12.

38. Wells M The pathology of gestational trophoblastic disease: recent advances Pathology. 2007 Feb;39(1):88-96.

39. Seckl MJ, Gillmore R, Foskett M, Sebire NJ, Rees H, Newlands ES. Routine terminations of pregnancy--should we screen for gestational trophoblastic neoplasia? Lancet. 2004 Aug 21-27;364:705-7.

40. Berry E, Hagopian GS, Lurain JR. Vaginal metastases in gestational trophoblastic neoplasia.J Reprod Med. 2008 Jul;53(7):487-92.

41. Pezeshki M, Hancock BW, Silcocks P, Everard JE, Coleman J, Gillespie AM, The role of repeat uterine evacuation in the management of persistent gestational trophoblastic disease.Gynecol Oncol. 2004 Dec;95(3):423-9.

42. Sebire NJ, Foskett M, Short D, Savage P, Stewart W, Thomson M, Seckl MJ Shortened duration of human chorionic gonadotrophin surveillance following complete or partial hydatidiform mole: evidence for revised protocol of a UK regional trophoblastic disease unit.BJOG. 2007 Jun;114(6):760-2.

43. Yedema KA, Verheijen RH, Kenemans P, Schijf CP, Borm GF, Segers MF, Thomas CM.Identification of patients with persistent trophoblastic disease by means of a normal human chorionic gonadotropin regression curve.Am J Obstet Gynecol. 1993 Mar;168:787-92.

44. Limpongsanurak S. Prophylactic actinomycin D for high-risk complete hydatidiform mole , J Reprod Med. 2001 Feb;46(2):110-6.

45. Costa HL, Doyle P, Influence of oral contraceptives in the development of post-molar trophoblastic neoplasia--a systematic review.Gynecol Oncol. 2006 Mar;100(3):579-85. Epub 2005 Nov 17.

46. Stone M, Bagshawe KD. An analysis of the influences of maternal age, gestational age, contraceptive method, and the mode of primary treatment of patients with hydatidiform moles on the incidence of subsequent chemotherapy. Br J Obstet Gynaecol. 1979 Oct;86(10):782-92.

47. Berkowitz RS, Goldstein DP. Clinical practice. Molar pregnancy. N Engl J Med. 2009 Apr 16;360(16):1639-45.

48. Behtash N, Ghaemmaghami F, Honar H, Riazi K, Nori A, Modares M Is normal beta-hcg regression curve helpful in the diagnosis of persistent trophoblastic disease?Int J Gynecol Cancer. 2004 Sep-Oct;14(5):980-3.

49. Alazzam M, Tidy J, Hancock BW, Osborne R.Cochrane Database Syst Rev. 2009 Jan 21;(1):CD007102.First line chemotherapy in low risk gestational trophoblastic neoplasia.

50. McGrath S, Short D, Harvey R, Schmid P, Savage PM, Seckl MJ. The management and outcome of women with post-hydatidiform mole 'low-risk' gestational trophoblastic neoplasia, but hcg levels in excess of 100 000 IU l(-1).Br J Cancer. 2010 Mar 2;102(5):810-4. Epub 2010 Feb 16.

51. Bower M, Newlands ES, Holden L, Short D, Brock C, Rustin GJ, Begent RH, Bagshawe KD. EMA/CO for high-risk gestational trophoblastic tumors: results from a cohort of 272 patients J Clin Oncol. 1997 Jul;15(7):2636-43.

52. Wang J, Short D, Sebire NJ, Lindsay I, Newlands ES, Schmid P, Savage PM, Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE).Ann Oncol. 2008 Sep;19(9):1578-83. Epub 2008 May 2.

53. Schmid P, Nagai Y, Agarwal R, Hancock B, Savage PM, Sebire NJ, Lindsay I,Prognostic markers and long-term outcome of placental-site trophoblastic tumours: a retrospective observational study.Lancet. 2009 Jul 4;374(9683):48-55.

54. Woolas RP, Bower M, Newlands ES, Seckl M, Short D, Holden L. Influence of chemotherapy for gestational trophoblastic disease on subsequent pregnancy outcome Br J Obstet Gynaecol. 1998 Sep;105(9):1032-5.

55. Rustin GJ, Newlands ES, Lutz JM, Holden L, Bagshawe KD, Hiscox JG, Foskett M, Fuller S, Short D. Combination but not single-agent methotrexate chemotherapy for gestational trophoblastic tumors increases the incidence of second tumors.J Clin Oncol. 1996 Oct;14(10):2769-73.

56. Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C. Epidemiology and aetiology of gestational trophoblastic diseases. Lancet Oncol. 2003 Nov;4:670-8

57. Shi YF, Li JQ, Zheng W, Chen XJ, Qiao YH, Hao M, Zhou CW, Survey of gestational trophoblastic disease incidence among 3.6 million pregnancies in China.Zhonghua Fu Chan Ke Za Zhi. 2005 Feb;40(2):76-8.

58. Fatima M, Kasi PM, Baloch SN, Kassi M, Marri SM, Incidence, management, and outcome of molar pregnancies at a tertiary care hospital in quetta, pakistan.ISRN Obstet Gynecol. 2011;:925316. Epub 2011 Oct 16.

59. Smith HO, Wiggins C, Verschraegen CF, Cole LW, Greene HM, Muller CY, Qualls CR.Changing trends in gestational trophoblastic disease ,J Reprod Med. 2006 Oct;51(10):777-84.

60. Soares PD, Maesta I, Costa OL, Charry RC, Dias A, Rudge MV,Geographical distribution and demographic characteristics of gestational trophoblastic disease. J Reprod Med 2010 Jul-Aug;55(7-8):305-10.

61. Altman AD, Bentley B, Murray S, Bentley JR. Maternal age-related rates of gestational trophoblastic disease. J Obstet Gynecol. 2008 Aug;112(2 Pt 1):244-50.

62. Soto-Wright V, Bernstein M, Goldstein DP, Berkowitz RS. The changing clinical presentation of complete molar pregnancy Obstet Gynecol. 1995 Nov;86(5):775-9.

63. Palmer JE, Macdonald M, Wells M, Hancock BW, Tidy JA Epithelioid trophoblastic tumor: a review of the literature.J Reprod Med. 2008 Jul;53:465-75.

64. Smith HO, Qualls CR, Prairie BA, Padilla LA, Rayburn WF, Key CR Trends in gestational choriocarcinoma: a 27years perspective, Obstet Gynecol. 2003 Nov; 102(5 Pt 1):978-87.

65. Sebire NJ, Foskett M, Paradinas FJ, Fisher RA, Francis RJ, Short D, Newlands ES, Seckl MJ. Outcome of twin pregnancies with complete hydatidiform mole and healthy co-twin.Lancet. 2002 Jun 22;359(9324):2165-6.

66. Seckl MJ, Dhillon T, Dancey G, Foskett M, Paradinas FJ, Rees HC, Sebire N, Vigushin DM, Newlands ES.Increased gestational age at evacuation of a complete hydatidiform mole: does it correlate with increased risk of requiring chemotherapy? J Reprod Med. 2004 Jul;49(7):527-30.

67. Kang WD, Choi HS, Kim SM. Weekly methotrexate (50mg/m(2)) without dose escalation as a primary regimen for low-risk gestational trophoblastic neoplasia. Gynecol Oncol. 2010 Jun;117(3):477-80. Epub 2010 Mar 29.

68. Osborne RJ, Filiaci V, Schink JC, Mannel RS, Alvarez Secord A, Kelley JL, Phase III trial of weekly methotrexate or pulsed dactinomycin for low-risk gestational trophoblastic neoplasia: a gynecologic oncology group study.J Clin Oncol. 2011 Mar 1;29(7):825-31. Epub 2011 Jan 24.

69. Q. K. Lippmann, R. K. Hanna, J. T. Soper, Single-agent methotrexate for low-risk gestational trophoblastic disease, 2011 ASCO Annual Meeting, J Clin. Oncol 29: 2011

70. Lurain JR, Singh DK, Schink JC. Management of metastatic high-risk gestational trophoblastic neoplasia: FIGO stages II-IV: risk factor score > or = 7. J Reprod Med. 2010 May-Jun;55(5-6):199-207.

71. Oluwole F, Vinita P,, Maria L C,Pei H,Epithelioid trophoblastic tumor clinicopathological features with emphasis on uterine cervical involvement, Modern Pathology (2006) ,19, 75-82.

ANNEXURES

PROFORMA

1. Name Age IP No

   Address & Phone No.

2. Clinical Presentation
   - Gravida Para live births abortions
   - months of amenorrhea
   - Bleeding p/v
   - Detected without any complaint on ultrasound
3. Associated Complaints -anaemia
   - Hyperemesis
   - Hypertension
   - Thyroid Symptoms
   - Embolic symptoms
   - metastatic symptoms
4. Gestational Age at the time of Diagnosis
   - Uterine size in relation with gestational age
5. Menstrual History

   Menarche Cycles Flow LMP
6. Obstetric History
   - Gravida Para Live births Abortions
   - previous molar pregnancy
   - h/o contraceptive use
7. Past Medical History
8. Family History
   - h/o molar pregnancies in other wives of husband

9. Personal History

10. General Examination

    height weight BMI

    pallor hydration status icterus

    Pulse rate BP

    PS BSA

11. Physical Examination

    Cardio vascular and Respiratory system

    Abdominal examination before and after evacuation

    uterine size

    Theca leutin cysts and size

    Bimanual pelvic examination

12. Investigations

- Serum ß HCG
- Ultrasound abdomen and pelvis and doppler if required
- Chest X-ray
- Complete hemogram
- Blood grouping and typing
- Renal and liver function tests
- Thyroid function tests
- CT Brain ,abdomen if required

13. Evacuation Details

14. Histopathology Report

15. Chemotherapy Details (if given)

16. Follow Up

ABBREVIATIONS

GTD	-	Gestational Trophoblastic diseases
CM	-	Complete mole
PM	-	Partial mole
CC	-	choriocarcinoma
PSTT	-	Placental site trophoblastic tumor
ETT	-	Epithelioid trophoblastic tumor
GTN	-	Gestational trophoblastic neoplasia
βhcg	-	human chorionic gonadotrophin
hPL	-	human placental lactogen
mIU/ml	–	milli international units/milliliter
IT	-	intermediate trophoblast
IU/L	-	international units/liter
LH	-	Luteinizing hormone
FIGO	-	International Federation of Gynecology and Obstetrics
WHO	–	World Health Organisation
CT	-	Computed Tomography
MRI	-	magnetic resonance imaging
FDG PET -2,	-	fluro deoxy glucose positron emission tomography
PTD	–	Persistent trophoblastic tumor
Cms	-	Centimeters
RCOG	–	Royal College of Obstetrics and Gynecology
GTG	-	Green top guidelines
ACOG	-	American College of Obstetrics and Gynecologists
GOG	-	Gynecology Oncology Group
NETDC	–	New England Trophoblastic Disease Center

OCP	–	Oral Contraceptive Pills
SPSS	-	Statistical Programme for Social Sciences
mg	-	milligram
EMA-CO	–	Etoposide , Methotrexate , Actinomycin , Cyclophosphamide , Oncovin
EMA –EP	-	Etoposide , Methoterxate , Actinomycin , Etoposide , Cisplatin
VIP	-	Vinblastin , Ifosfamide , Cisplatin
ICE	-	Ifosfamide , Carboplatin , Etoposide
TE/TP	–	Paclitxol , Etoposide , Cisplatin
PEB	-	Cisplatin , Etoposide, Bleomycin
RR	-	Relative Risk
IOG	-	Institute of Obstetrics and Gynecology
KMC	–	Kilpauk medical College
ISO KGH	–	Institute of Social Obstetrics , Kasturibai Gandhi Hospital
SMC	–	Stanley medical college
GH	-	Government Hospital
GA	-	Gestational age
cGY	–	centiGray
g	-	grams
sq.m	-	square meter
HLA	-	human leucocyte antigen
ANA	–	Antinuclear antibody
AION	–	Anterior ischemic optic neuropathy
HIV	–	Human Immunodeficiency Virus
HbS Ag+ve	-	Hepatitis B surface antigen positive
AML	–	Acute myeloid leukemia
UK	-	United kingdom

INFORMED CONSENT

PART 1

STUDY TITLE: **"**Prospective study of natural history, follow up, treatment and outcome of patients with Gestational trophoblastic disease attending IOG".

STUDY CENTRE: Department of Obstetrics and Gynecology, Institute of Obstetrics and Gynecology, Egmore, Chennai- 8.

PARTICIPATE NAME**:** AGE ADDRESS**:** IP/ OP NO:

INFORMATION SHEET

Gestational trophoblastic disease includes molar pregnancies and related disorders which are due to abnormal fertilization of egg, with no formation of the baby and results in multiplication of placenta forming trophoblastic cells.

Suction evacuation is the treatment after initial evaluation with blood tests, chest xray and ultrasound. Since there is a risk of malignant disease after evacuation, all patients with molar pregnancies after evacuation are followed up with serum β hcg at regular intervals. It is necessary to use contraception (oral contraceptive pills or codomn) in the follow up period.

If malignancy is detected in the follow up period, it is completely curable with chemotherapy regimens and future fertility is well preserved.

All patients will be treated according to hospital guidelines and protocols.

The study is being performed for the estimation of incidence, natural history, treatment, follow up and outcome of patients with gestational trophoblastic disease attending IOG.

PART 2

I confirm that I have read and understood the Information Sheet for the above study and the purpose of the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the study details. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties of published, unless as required under the law. I agree not to restrict the use of any or results that arise from the study.

I hereby give permission to undergo complete clinical examination diagnostic tests including hematological, biochemical, and radiological tests.

I have been informed that I will be given treatment according to the cause as per the hospital guidelines

I hereby consent to participate in this study of Prospective study of natural history, follow up, treatment and outcome patients with Gestational trophoblastic disease attending IOG.

Signature / Thumb impression of patient Place Date

Name and Signature of witness Place Date

Study Investigators Name

Signature of Investigator Place Date

Institution:

Guide

Ra xgg[j y; go t k;

Ma;t[braa,aggLk; j i ygg[: Kj;Jgg,s;is neha,d; t,f,jk; ,ayg[jd;ik r,f,r;ir Kiw bjhlh; f z;fhz,gg[kw,Wk; r,f,r;ir gyd; gw,w,a v,jh,nehf,F Ma;t[

Ma;t[braa,aggLk; , lk; : muR kfgnghW kUj;Jtkid. vGkg{h; brd;id/

Ma;t,y; g'F bgWgth,d; bgah; : taJ nehahs, vz;

Kfth,

gFj, ? 1 nehahs,a,d; jfty; gotk;

Gestational Trophoblastic Disease vdgJ Kj;Jg,s;is kw,Wk; mjd; rhh,e;j neha;fs; cs,sl';f,aJ/ Kj;J g,s;is neha; rh,ahd Kiwa,y; fUj;jh,f;fhjjhy; FHe;ijfs; cWgg[fs; cUthfhky; e"Rf; bfho j,Rf;fs; kl;Lk; mj,fkhf tsUk; xU neha/

,jw;F ,uj;jggh,nrhjid. !nfd; khhgG; gFj, vf;!nu gh,nrhjidfis bra;j g,wF cw,"R FHha; Kyk; Kj;Jg,s;isia bts,na mfw,Wtnj ,jw;Fh,a r,f,r;irahFk/

Kj;Jg,s;is neha; te;j r,yUf;F mJ g[w,W nehahf khWtjw;fhd thagg[cs,sJ/ ,jdhy; bjhlh; fz;fhz,gg[r,f,r;ir k,ftL k; mtr,ak/ cly; gh,nrhjid βhcg ,af;Feh; gh,nrhjid. !nfd; Mf,atw;iw rh,ahd ,ilbts,a,y; njitahd bghGJ bra;J bfhz;lhy; g[w,W nehia Mukg e,iya,nyna fz;lw,e;J t,lyhk/

,e;j g[w,Wneha;f;F kUe;Jfs; Kyk; vs,jhf r,f,r;ir bra;J KGjhf Fzkila thagg[cs,sJ/ bjhlh; fz;fhz,gg[r,f,r;ir braa[k,nghJ khjhe;j,u fUj;jil khj;j,iufs; my,yJ MQ,iw Mf,a fUj;jil Kiwfis cgnahf,ggJ mtr,ak/ r,f,r;ir Koe;j g,d; fUj;jUgg,nyh. FHe;ij bgWtj,nyh vt;t,j g,urr,idaL k; VwglhJ/,kkUj;Jtkida,d; t,j,fSf;Flgl;L Kj;Jg,s;is neha;f;fhd r,f,r;ir ms,f;fggLk/

,e;j v,jh,nehf;F Ma;t[Kj;Jg,s;isa,d; neha,d; t,f,jk; ,ayg[. jd;ik. r,f,r;ir Kiw bjhlh;fz;fhz,gg[kw,Wk; r,f,r;ir gyd; mw,tjw;fhf nkwbfhs,sggLf,wJ/ ,e;j Ma;t,dhy; vt;t,j gh,jggL k; ,y;iy/

gFj; 22

vdf;F Kj;Jggps;is neha; gwwp vLj;Jf; Twggl;lJ/ mjd; rpfpr;ir Kiwfis gwwp tpsf;fk; mspf;fggl;lJ/ vd;Dila renjf';fis nfl;ftpk; mjw;fhd jFe;j tpsf;f';fis bgwtpk; thaggspf;fggl;lJ.

ehd; ,t;thaggpy; jd;dpr;irahfj;jhd; g'nfw;fpnwd/ ve;j fhuzj;jpdhnyh ve;j flljj;jYk; ve;j rl;l rpf;fYf;Fk; clglhky; ehd; ,t;tha;tpy; ,Ue;J tpyfp bfhss;syhk; vd;Wk; mwpe;J bfhznld/

,e;j Ma;t[rkke;jkhfnth. ,ij rhhpe;j nkYk; Ma;t[nkwbfhs;Sk; nghJk; ,e;j Ma;tpy; g';F bgWk; kUj;Jth; vd;Dila kUj;Jt mwpf;iffis ghhggjw;F vd; mDkjp njitapy;iy vd mwpe;J bfhs;fpnwd/ ehd; Ma;tpy; ,Ue;J tpyfp bfhz;lhYk; ,J bghUe;Jk/ vd mwpfpnwd/

,e;j Ma;tpd; Kyk; fpilf;Fk; jfty;fisapk; ghpnrhjid Kotpfis kw;Wk; rpfpr;ir bjhlhghd jfty;fisapk; kUj;Jth; nkwbfhs;Sk; Ma;tpy; gadgLj;jpf; bfhss;stpk; mij gupRhpf;ftpk; vd; KGkdJld; rkkjpf;fpnwd/

,e;j Ma;tpy; g';F bfhss; xggpfbfhs;fpnwd/ vdf;F bfhLf;fggl;l mwpt[iufspdgo ele;J bfhs;tJld; ,e;j Ma;it nkwbfhs;Sk; kUj;Jt mzpf;F cz;ikapld; ,Ugnghd; vd;Wk; cWjpapspf;fpnwd/ vd; cly; eyk; ghjpf;fggl;lhnyh myyJ vjphghuhj tHf;fj;jpw;F khwhd neha;f;Fwp bjdgl;lhnyh clnd mij kUj;Jt mzpaplk; bjhptpgnghd; vd cWjp mspf;fpnwd/

,e;j Ma;tpy; vdf;F ,uj;jk; !nfd; vf;!nu ghpnrhjid bra;J bfhss; ehd; KG kdJld; rkkjpf;fpnwd/

g'nfwgthpd; ifbahggk; - fl;il tpuy; nuif /////////// ,lk; ////////////////// njjp

rhl;rpahshpd; bgah; ifbahggk; /////////// ,lk; ////////////////// njjp

Ma;thshpd; bgah; ifbahggk/////////// ,lk; ////////////////// njjp

MASTER CHART

S NO.	Reg No.	Age(years)	parity	Symptoms	Complication	period of Gestation	Uterine Size(weeks)	Ultra Sound	Chest Xray	βhCG (mIU/ml)	weeks to Normal	HPE	GTN	WHO Score	Treatment	follow up	Referral
1	112/10	23	G3P2L2	USG	cough anemia	3MA	12	CM, B/L TLC	N	471,622	19	CM	GTN	0	SE/MTX11	ND 1 year	IOG
2	115/10	19	primi	Bleeding	-	3 MA	18	CM	N	299463	16	CM	-	-	SE	ND 6mon	IOG
3	116/10	19	primi	USG	-	3MA	20	CM	N	217653	11	CM	-	-	SE	ND 4 mon	IOG
4	118/10	27	G2P1L1	Spotting	vomiting	4MA	12	PM	N	41000	31	PM	GTN	1	SE/MTX4/ Act2	ND 10 mon	KGH
5	119/10	20	P1L1 (FTND)	Bleeding	Giddiness, headache, vomitting	FTND	12	? Retained POC	mets	16480	-	-	high risk GTN	10	EMACO,RT	expired	Arakkonam GH
6	126/10	23	G2P1L1	Missed abortion	AION of right eye	3MA	18	Retained POC	N	15530	8	-	GTN	1	SE/MTX7/ Act2	ND 6mon, pregnant	SMC
7	130/10	20	G2P1L1	USG	vomiting , anemia	3MA	12	CM	N	225000	16	CM	-	-	SE	ND 10 mon	IOG
8	131/10	29	G3P2L1	USG	-	3MA	12	CM	N	225000	24	CM	GTN	1	SE/ MTX3/ Act5	ND 9 mon	IOG
9	132/10	26	G3P2L1	USG	Spotting after SE, cough wheeze	3MA	12	CM	N	18110	12	CM	GTN	1	SE/MTX8	ND 1year	KGH
10	133/10	25	G3P1L1A1	Bleeding	anemia	3MA	18	CM, BL - TLC	N	1430	12	CM	-	-	SE	ND 3 mon	IOG
11	135/10	25	G3P1L1A1	Foul smelling discharge	LCB - 10 yrs	12 MA	24	Multiple Air pockets in Ut.	N	50938	32	ETT	GTN	5	TAH/MTX10	ND 3 mon pregnant	IOG
12	137/10	21	G2A1	Spotting	anemia	3 MA	16	CM	N	500000	19	CM	GTN	6	SE/MTX10	ND 11 mon	Pvt
13	139/10	19	primi	Bleeding	vomiting	5MA	20	CM	N	140000	-	C. mole	-	-	SE	defaulter	IOG
14	143/10	27	G2P1L1	USG DCDA twins fetus with CM	anemia ,PIH	8MA	28	fetus with CM	N	24888	8	CM	-	-	LN/ SE	ND 10 mon	IOG
15	145/10	25	G3P2L2	Bleeding	rpt SE	3MA	20	PM	N	13409	-	PM	-	-	SE	Defaulter	IOG
16	146/10	21	primi	Spotting	-	3MA	20	CM	N	200000	-	CM	-	-	SE	Defaulter	IOG
17	148/10	32	G2P1L1	Bleeding	Invasive mole	2MA	16	PM	N	55440	24	PM	GTN	2	SE/MTX9/ Act5	ND 10 mon	IOG
18	149/10	18	primi	Spotting	vomiting, anemia	3MA	16	PM	N	3350	8	PM	-	-	SE	ND 1year	IOG
19	151/10	25	G3P2L2	Bleeding	-	4MA	20	CM	N	139108	17	CM	-	-	SE	ND 10 mon	IOG
20	152/10	20	primi	USG	-	2MA	10	PM	N	3767	8	PM	-	-	SE	ND 5 mon pregnant	IOG
21	156/10	33	G2P1L1	Bleeding	anemia	2MA	24	CM	N	150000	-	CM	-	-	SE	Defaulter	IOG
22	160/10	22	G2P1L1	Bleeding	-	2MA	12	CM	N	39882	8	CM	-	-	SE	ND 1year	IOG
23	169/10	21	primi	Bleeding	-	3MA	16	CM	N	10290	8	CM	-	-	SE	ND 1 year	IOG
24	170/10	24	G2P1L1	Bleeding	Bleeding, invasive mole	2MA	10	CM	N	35,509	28	CM	GTN	2	SE/MTX11/ Act2	Quiescent disease	IOG
25	171/10	23	G3P2L2	spotting	-	5 MA	18	CM	N	172966	12	CM	-	-	SE	Defaulter	IOG
26	176/10	25	G2P1L1	spotting	anemia	3 MA	16	CM	N	4,69,525	16	CM	-	-	SE	ND 8 mon	IOG
27	177/10	22	primi	spotting	vomiting ,	3 MA	12	CM	N	413862	16	CM	-	-	SE	ND 8 mon	IOG
28	180/10	23	G3A2	spotting	vomiting repeat mole	3MA	12	CM	N	12900	28	CM	GTN	3	SE/MTX6/ Act4 PEB4	ND 9mon	IOG
29	181/10	17	primi	bleeding	vomiting cough anemia	3MA	24	CM	N	431088	-	CM	-	-	SE	defaulter	IOG
30	187/10	21	primi	Bleeding	-	3MA	16	CM	N	97,346	12	CM	-	-	SE	ND 10 mon	IOG
31	188/10	27	G3P1L1A1	Bleeding	-	2MA	10	PM	N	3124	8	PM	-	-	SE	ND 10 mon	IOG
32	191/10	18	primi	USG	-	4MA	20	CM	N	5,00,000	-	CM	-	-	SE	defaulter	IOG
33	192/10	30	G2P1L1	USG	anemia,RHD	2MA	16	PM	N	1,81,847	8	PM	-	-	SE	ND 11 mon	IOG
34	200/10	22	primi	bleeding	BA	2MA	10	CM	N	2,25,000	16	CM	-	-	SE	ND 9 mon	IOG
35	202/10	23	G2P1L1	spotting	-	3 MA	16	PM	N	3078	16	PM	-	-	SE	ND 9 mon	IOG
36	204/10	19	primi	bleeding	-	4MA	16	CM	N	3,27,364	-	CM	-	-	SE	Defaulter	IOG
37	207/10	32	G3P2L2	USG	vomiting	3MA	12	PM	N	37155	12	PM	-	-	SE	ND 10 mon	IOG

MASTER CHART

S NO.	Reg No.	Age(years)	parity	Symptoms	Complication	period of Gestation	Uterine Size(weeks)	Ultra Sound	Chest Xray	βhCG (mIU/ml)	weeks to Normal	HPE	GTN	WHO Score	Treatment	follow up	Referral
38	210/10	23	G2P1L1	USG	Anaemia	4MA	16	CM/TLC(B/L)	N	6245	-	CM	-	-	SE	defaulter	IOG
39	214/10	23	primi	USG	-	4MA	16	CM	N	1,13,657	-	CM	-	-	SE	defaulter	IOG
40	219/10	26	P1L1A1 (FTLSCS)	bleeding, breathlessness	vaginal nodule	FTLSCS	10	?retained POC	mets	2,25,000	40	-	high risk GTN	17	EMACO , RT	ND 3 mon	KGH
41	220/10	21	primi	USG	vomiting	3MA	12	CM	N	118175	9	CM	-	-	SE	ND 6 mon	IOG
42	223/10	23	G2P1L1	USG	Anemia, bicornuate ut	3MA	12	CMin both horns	N	2,25,000	12	CM	-	-	SE	ND 8 mon	IOG
43	226/10	25	G3P2L2	USG	RHD	5MA	20	CM	N	11582	10	CM	-	-	SE and intervel TAT	ND 6 mon	IOG
44	236/10	24	G4P3L2	bleeding	-	3MA	16	PM	N	35,220	16	PM	-	-	SE	ND 6 mon	IOG
45	238/10	21	G2P1L0	bleeding	anaemia	3MA	12	CM	N	2,76,739	11	CM	-	-	SE	ND 6 mon	IOG
46	245/10	22	G2P1L1	bleeding	anaemia	4MA	20	CM,B/L TLC	N	4,61,314	16	CM	-	-	SE	ND 4 mon	IOG
47	247/10	28	G3A2	Spotting	Repeatmole,HIV+ve	2MA	10	PM	N	196042	8	PM	-	-	SE	ND 6 mon	IOG
48	252/10	23	G2A1	bleeding	-	2MA	10	CM	N	136164	9	CM	-	-	SE	ND 6 mon	IOG
49	259/10	42	G3 P2L2	USG	vomiting ,RHD	3MA	12	CM	N	271504	32	CM	-	-	SE	Nd 2 mon	IOG
50	261/10	22	G2P1L1	spotting	-	2MA	12	CM	N	4,16,581	40	CM	GTN	1	SE/ MTX4/ Act3	ND 1 mon	IOG
51	262/10	30	G2P1L1	spotting	vomiting	2MA	18	CM	N	5,00,000	16	CM	-	-	SE	ND 6 mon	IOG
52	270/10	21	G2P1L1	USG	-	2MA	10	CM	N	312214	8	CM	-	-	SE	ND 9 mon	IOG
53	274/10	21	primi	USG	-	3MA	10	CM	N	60189	-	CM	-	-	SE	Defaulter	IOG
54	276/10	19	Primi	USG	-	2MA	12	CM	N	56129	-	CM	-	-	SE	Defaulter	IOG
55	277/10	20	G2P1L1	bleeding	anemia	3MA	16	CM	N	100445	16	CM	-	-	SE	ND 6 mon	IOG
56	278/10	21	G3P2L2	bleeding	-	2MA	24	CM	N	113194	35	CM	GTN	0	SE/MTX 7	ND 1 mon	IOG
57	280/10	26	G3P1L1A1	USG	-	5MA	20	CM,doppler- invasive mole	N	40,200	18	CM	GTN	1	SE/MTX4	ND 8 mon	IOG
58	283/10	29	G3P1L1A1	bleeding	-	4MA	20	CM	N	27795	8	CM	-	-	SE	ND 7 mon	IOG
59	287/10	20	G2A1	USG	anemia	2MA	10	CM	N	12,451	17	CM	GTN	1	SE/ MTX 5 /EMACO3	ND 6 mon	pvt
60	289/10	20	G3A2	USG	anemia	5MA	20	CM	N	17,979	-	CM	-	-	SE	Defaulter	IOG
61	290/10	25	primi	USG	-	4MA	20	CM	N	367356	19	CM	GTN	0	SE/MTX 6	ND 5 mon	IOG
62	291/10	35	G2P1L0	USG	-	3MA	12	PM	N	34692	16	PM	-	-	SE	ND 5 mon	IOG
63	297/10	26	G2P1L1	USG	-	4MA	12	CM,B/L TLC	N	457360	-	CM	-	-	SE	Defaulter	IOG
64	298/10	23	primi	USG	-	3MA	12	PM	N	89,151	14	PM	-	-	SE	ND 5 mon	IOG
65	299/10	25	primi	USG	-	5MA	16	CM	N	12,253	10	CM	-	-	SE	ND 5 mon	IOG
66	300/10	22	G4P2L1A1	spotting	-	4MA	24	CM	N	5,00,000	-	CM	-	-	SE	Defaulter	IOG
67	301/10	26	G4P1L1A1	bleeding	-	2MA	10	CM	N	2,17,681	19	CM	GTN	2	SE/ MTX 8	ND 6 mon	pvt
68	136/01	21	G4A3	USG	repeat mole	5MA	20	CM,Invasive mole,B/L TLC	N	5,00,000	-	CM	GTN	3	SE/MTX 3	on treatment	IOG
69	o1/11	20	primi	USG	-	2MA	12	PM	N	2560	12	PM	-	-	SE	ND 4 mon	IOG
70	o2/11	20	G2A1	USG	bicornuate uterus	2MA	12	CMin left horn of bicornuate uterus	N	1850	9	CM	-	-	SE	ND 4 mon	IOG
71	o4/11	30	G4P1L1A2	USG	-	3MA	12	CM	N	2,40,898	25	CM	-	-	SE	ND 4 mon	IOG
72	o5/11	20	G2A1	USG	anemia	2 MA	12	CM	N	36,947	9	CM	-	-	SE	ND 4 mon	IOG
73	o6/11	22	primi	USG	-	2MA	10	PM	N	18628	8	PM	-	-	SE	ND 5 mon	IOG

MASTER CHART

S NO.	Reg No.	Age(years)	parity	Symptoms	Complication	period of Gestation	Uterine Size(weeks)	Ultra Sound	Chest Xray	βhCG (mIU/ml)	weeks to Normal	HPE	GTN	WHO Score	Treatment	follow up	Referral
74	o7/11	22	G3P1L1A1	USG	repeat mole	2MA	16	CM,B/L TLC	N	2,00,000	22	CM	GTN	2	SE/MTX2/ EMACO 5	ND 3 mon	pvt
75	o8/11	26	primi	spotting	vomiting	3MA	20	CM	N	5,00,000	14	CM	-	-	SE	ND 2 mon	IOG
76	o9/11	25	G3 P2L2	bleeding	-	3MA	16	CM	N	2408	8	CM	-	-	SE	ND 2 mon	IOG
77	10/,11	20	G2P1L1	USG	vomiting	2MA	20	CM	N	1,50,000	-	CM	-	-	SE	Defaulter	IOG
78	12/,11	19	G3P1L1A1	USG	rpt SE	2MA	12	CM,B/L TLC	N	12,440	-	CM	GTN	0	SE/MTX5	defaulter(april)	pvt
79	14/11	20	G2P1L0	USG	RHD	2MA	10	PM	N	9260	8	PM	-	-	SE	ND 5 mon	IOG
80	19/11	25	G2P1L1	bleeding	vomiting	3MA	12	CM	N	36,566	8	CM	-	-	SE	ND 4 mon	IOG
81	20/11	25	G2P1L1	USG	USG prominent vascularity	3MA	20	Invasive mole	N	5,00,000	25	CM	GTN	2	SE/EMACO5	ND 4 mon	IOG
82	23/11	23	primi	spotting	vomiting ,HbsAg +ve	3MA	12	PM	N	3,920	12	PM	-	-	SE	ND 5 mon	IOG
83	31/11	25	primi	USG	-	2MA	10	CM	N	2,77,871	9	CM	-	-	SE	ND 4 mon	IOG
84	33/11	22	G2P1L1	USG	vomiting	3MA	16	CM ,B/L TLC	N	49,272	12	CM	-	-	SE	ND 4 mon	IOG
85	38/11	22	G3P1L1A1	USG	-	3MA	18	CM	N	4,00,000	9	CM	-	-	SE	ND 3 mon	IOG
86	39/11	22	G2P1L1	USG	-	2MA	10	CM	N	5,00,000	16	CM	-	-	SE	ND 1 mon	IOG
87	40/11	26	G2P1L1	spotting	anemia	3MA	16	CM	N	4,25,125	9	CM	-	-	SE	ND 3 mon	IOG
88	41/11	21	primi	USG	-	3MA	12	PM	N	7750	18	PM	GTN	0	SE/MTX3/ EMACO4	ND 4 mon	Pvt
89	44/11	20	G2P1L1	USG	-	4MA	20	CM	N	3,49,235	16	CM	-	-	SE	ND 3 mon	IOG
90	45/11	20	primi	USG	-	2MA	10	CM	N	3943	10	CM	-	-	SE	ND 4 mon	IOG
91	50/11	23	primi	USG	-	2MA	10	CM	N	116712	10	CM	-	-	SE	ND 4 mon	IOG
92	62/11	20	primi	USG	-	2MA	10	CM	N	2,08,820	10	CM	-	-	SE	ND 2 mon	IOG
93	63/11	28	G3P1L1A1	USG	-	3MA	12	CM	N	319,281	12	CM	-	-	SE	ND 4 mon	IOG
94	64/11	24	G3P2L1	spotting	-	4MA	12	PM	N	18,724	8	PM	-	-	SE	ND 3 mon	IOG
95	66/11	26	G3 P2L2	bleeding	vomiting	4MA	12	CM	N	91,131	8	CM	-	-	SE	ND 4 mon	IOG
96	70/11	29	G2P1L1	bleeding	-	4MA	18	CM	N	24,176	13	CM	-	-	SE	ND 3 mon	IOG
97	71/11	32	G2P1L1	bleeding	-	2MA	10	PM	N	3,833	9	PM	-	-	SE	ND 4 mon	IOG
98	75/11	19	primi	USG	-	2MA	10	CM	N	5,000	8	CM	-	-	SE	ND 1 mon	IOG
99	76/11	26	G3P2L1	spotting	-	3MA	12	PM	N	14,899	14	PM	-	-	SE	ND 3 mon	iOG
100	77/11	22	G3P2L1	Bleeding	-	2MA	10	CM	N	2,612	10	CM	-	-	SE	ND 3 mon	IOG
101	78/11	20	primi	USG	-	4MA	16	CM	N	2,70,714	12	CM	-	-	SE	ND 2 mon	IOG
102	79/11	26	G4P1L1A2	bleeding	vomiting	4MA	10	PM	N	1,68,532	8	PM	-	-	Se	ND 2 mon	IOG
103	86/11	27	G2P1L1	spotting	vomiting	5MA	16	CM	N	73,444	9	CM	-	-	SE	ND 2 mon	IOG
104	87/11	18	primi	USG	-	3MA	20	CM	N	10,003	9	CM	-	-	SE	ND 3 mon	IOG
105	89/11	22	G3P2L2	spotting	-	5MA	18	CM	N	7,654	8	CM	-	-	SE	ND 2 mon	IOG
106	90/11	27	G2P1L1	USG	-	3MA	16	CM	N	7,143	8	CM	-	-	SE	ND 3 mon	IOG
107	91/11	28	primi	USG	vomiting	4MA	10	CM	N	1,87,722	8	CM	-	-	SE	ND 2 mon	IOG
108	94/11	20	primi	USG	-	4MA	16	CM	N	4,57,439	12	CM	-	-	SE	ND 1 mon	IOG
109	98/11	24	G3P2L1	spotting	--	3MA	12	CM	N	5,00,000	10	CM	-	-	SE	ND 1 mon	IOG
110	101/11	23	G2P1L1	bleeding	-	4MA	20	CM	N	2,25,000	-	CM	-	-	SE	defaulter	IOG
111	102/11	23	primi	USG	-	3MA	16	PM	N	6,579	12	PM	-	-	SE	ND 3 mon	IOG
112	103/11	30	G6P4L4A1	spotting	-	3MA	12	CM	N	9,065	8	CM	-	-	SE	ND 3 mon	IOG
113	104/11	23	primi	USG	-	3MA	12	CM	N	1,12,000	10	CM	-	-	SE	ND 2 mon	IOG
114	159/10	26	G3P1L1A1	bleeding	rpt SE	5MA	20	CM	N	7912	21	GTN	GTN	1	SE/MTX9	ND 10 mon	KMC

KEY TO MASTER CHART

G3P1L1A1	-	Gravida 1, Para 1, Live birth 1, Abortion 1
FTND	–	full term normal delivery
FTLSCS	–	full term lower segment caesarean section
USG	–	Ultrasound
DCDA	-	Dichorionic Diamniotic
AION	-	Anterior ischemic optic neuropathy
SE	-	Suction Evacuation
Rpt	-	Repeat
LCB	-	last child birth
PIH	-	pregnancy induced hypertension
POC	-	Products of conception
RHD	-	Rheumatic heart disease
BA	-	Bronchial asthma
HIV	-	Human immunodeficiency virus
HbSAg	-	Hepatitis B surface Antigen positive
MA	-	months of amenorrhea
CM	-	Complete mole
PM	-	Partial mole
B/L	-	bilateral
TLC	-	Theca leutin cysts

Ut	-	uterus
N	-	Normal
Mets	-	metastasis
TAH	-	Total abdominal hysterectomy
hcg	-	human chorionic gonadotrophin
GTN	-	Gestational trophoblastic neoplasia
LN	-	Labour Natural
Act2	-	Actinomycin 2 cycles
Mtx 7	-	Methotrexate 7 cycles
EMA- CO	–	Etoposide, Methotrexate, Actinomycin, Cyclophosphamide, Oncovin
PEB	-	Cisplatin , Etoposide, bleomycin
RT	-	Radiotherapy
TAT	-	Transabdominal tubectomy
ND 2mon	-	Not detectable for 2 months
IOG	-	Institute of obstetrics and Gynecology
Pvt	-	private hospital
KGH	-	Kasturba Gandhi hospital
KMC	-	Kilpauk Medical College
SMC	-	Stanley medical College
GH	-	Government hospital